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One Health Triad

Editors:
Ahrar Khan, Rao Zahid Abbas, Liliana Aguilar-Marcelino, Nahla M Saeed and Muhammad Younus

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ONE HEALTH TRIAD

Volume 1

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EDITORS

VOLUME 1

AHRAR KHAN, Ph.D

Shandong Vocational Animal Science
and Veterinary College,
Weifang, China

RAO ZAHID ABBAS, Ph.D

Department of Parasitology,
Faculty of Veterinary Science,
University of Agriculture,
Faisalabad, Pakistan

LILIANA AGUILAR-MARCELINO, Ph.D

National Centre for Disciplinary Research
in Animal Health and Safety,
National Institute of Agricultural
and Forestry Research, Mexico

NAHLA MOHAMMED SAEED, Ph.D

Department of Microbiology,
College of Veterinary Medicine,
University of Sulaimania,
Kurdistan of Iraq

MUHAMMAD YOUNUS, Ph.D

University College of Veterinary
& Animal Sciences Narowal,
Pakistan

Unique Scientific Publishers ®

House No. 1122, St No. Liaquat Abad, Faisalabad-Pakistan.

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PREFACE

The well-being of humans and animals is pretty much interdependent. It's impossible to ensure human health, food security and food safety, and welfare without considering animal and environmental health.

The need to enhance the collaboration between animal health workers and medical professionals, researchers and academicians has moved the editors to develop this publication. The book takes into account the major threats of animal, human and environmental health. This book provides the core concepts of One Health approach with a critical focus on the key challenges i.e., zoonotic diseases and environmental degradation. The objective is to cover epidemiological interactions of various infectious diseases and their environmental and ecological implications as an emerging threat.

It is anticipated that this book would be of great use to a variety of readers. University students, graduates, practitioners, animal healthcare providers and health professionals would definitely find this book of great importance. The language of book has been intentionally kept easier for a non-technical person to grasp the concepts on interdependence of animal, human and environmental health. The editors wish to publish a series on the subject keeping in view the urgency to highlight these areas for awareness, research and development.

Editors

Contents

Sr.	Title	Page
1.	Climate Change and Its Role in the Emergence and Re-Emergence of Zoonotic Diseases that Increase the Risk of Future Pandemics Virginia Guadalupe García-Rubio, Juan José Ojeda-Carrasco, Enrique Espinosa-Ayala, Pedro Abel Hernández-García, Laura Dolores Rueda-Quiroz	1
2.	Impact of Climate Change on Animal Health Sayyed Aun Muhammad, Abdul Rauf, Hamza Ali and Muhammad Awais	8
3.	Repercussions of Climate Change on Zoonoses and Food Security Juan José Ojeda-Carrasco, Virginia Guadalupe García-Rubio, Laura Dolores Rueda-Quiroz, Pedro Abel Hernández-García, Enrique Espinosa-Ayala, Ofelia Márquez-Molina	14
4.	Climate Change and the Resulting Waterborne Diseases Arooba Mubeen, Syeda Ayesha Batool Bukhari, Ayesha Fakhri, Maryam Aziz	21
5.	Sustainable Control of Contaminated Water Hafiza Saba Javed and M. Adnan Sabir Mughal	25
6.	Impact of Emerging Pollutants on a Health Triad: Environment, Animals and Humans Pablo Antonio Moreno-Pérez, Gauddy Lizeth Manzanares-Leal, Miguel Ángel Karam Calderon, Yazmín Castillo Sánchez, Ninfa Ramírez-Durán	31
7.	Power of Positive Human Animal Relationship for Animal Welfare Faiza Bano, Aayesha Riaz, Murtaz Ul Hassan, Sohail Sajid, Nazia Rafiq, Muhammad Farooq Iqbal	36
8.	Global Warming: A Neglected Conundrum from One Health Perspective Muhammad Umair Waqas, Ifra Chaudhary, Kashif Hussain, Asghar Abbas, Atif Rehman, Baseer Ahmad, Muhammad Asif Raza, Junaid Ali Khan, Ali Haider, Ahsan Anjum, Waqar Zaib and Hafeez ur Rehman Ali Khera	45
9.	Impact of Plant-Originated Morin Hydrate on Human and Animal Health Shahid Ali Rajput, Aziz Ul Rahman, Rana Muhammad Shahbakht, Rana Waseem Akhtar, Ahsan Anjum, Atiq Ali, Asghar Abbas, Baseer Ahmad, Junaid Ali Khan, Muhammad Asif Raza and Aftab Shaukat	52
10.	Human Sleeping Sickness: A Challenge for Health Professionals Abdullah Azeem, Muhammad Kasib Khan, Nida Naazir, Muhammad Asad, Sundas Afresham, Muhammad Usman, Maryam Hanif and Muhammad Asif Razzaq	61
11.	Epidemiology and Public Health Risks Associated with Monkey Pox Sara Ijaz, M. Faizan Elahi Bhatti, Mamoona Arshad, Ammar Faiz, Aiman Mushtaq, Sana Shahid, Khushbakht Asad and Shama Jamil	66
12.	West Nile Virus- A Neuroinvasive Disease Muhammad Ali Tahir, Kashif Hussain, Asghar Abbas, Ali Haider, Baseer Ahmad, Ayesha Ramzan, Muhammad Muneeb, Shoaib Shafqat, Atif Rehman, Muhammad Umair Waqas, Riffat Yasin and Muhammad Asif Raza	71

13.	Covid-19 and Vaccine Hesitancy among Public Communities: A Global Health Perspective …………………………………… Aziz Ul-Rahman, Muhammad Abu Bakr Shabbir, Shahid Ali Rajput, Momena Habib, Naheed Bano, Ahsan Anjum, Nasir Niaz, Nusrat Shafi and Muhammad Asif Raza	80
14.	COVID-19 Pandemic: Its Public Health Concern and Economic Outcomes in Pakistan and Future Impact …………………………………… Maria Jamil, Aisha Khatoon, Muhammad Kashif Saleemi, Al-Hafiza Shafia Tehseen Gul, Muhammad Imran, Wafa Majeed, Ashiq Ali, Muhammad Yasir Nawaz, Aftab Shaukat	86
15.	Bat Borne Viral Zoonosis …………………………………… Ali Zohaib, Momina Ejaz, Anam Fatima, Saman Noor, Iman Fatima, Medhat Rehman and Aneela Javed	92
16.	Rotavirus Gastroenteritis: A Food-borne Viral Disease …………………… Waqar Zaib, Kashif Hussain, Qurratulain Amin, Rana Muhammad Shahbakht, Asghar Abbas, Safder Imran, Rabeea Sardar, Muhammad Umair Waqas, Muhammad Asif Raza, Junaid Ali Khan, Hafeez Ur Rehman Ali Khera and Shahwaiz Tariq	99
17.	Rabies: the Vet-verse of Madness …………………………………… Tayyaba Ameer, Shamreza Aziz, Irza, Muhammad Younus, Qamar un Nisa, Tayyaba Akhtar, Waqas Ahmad, Muhammad Ifham Naeem and Saim Shahbaz	106
18.	Public Health Risks Associated with Norovirus Gastroentritis …………………… Sara Ijaz, Shama Jamel, Ammar Faiz, Abdullah Alsayeqh, Aiman Mushtaq, M. Faizan Elahi Bhatti and Khushbakht Asad	116
19.	Zika Virus: A Pathological and Clinical Perspective …………………… Muhammad Imran, Munazza Aslam, Muhammad Kashif Saleemi, Shengbo Cao, Jing Ye, Al-Hafiza Shafia Tehseen Gul, Aisha Khatoon, Muhammad Wasim Usmani, Mughees Aizaz Alvi, Shah Nawaz, Muhammad Imran, Muhammad Ahsan Naeem, Maria Jamil	121
20.	Lumpy Skin Disease …………………………………… Muhammad Arif Zafar, Adnan Hassan Tahir and Muhammad Farhan Rahim	128
21.	Bovine Ephemeral Fever (BEF) …………………………………… Rehan Ashraf, Saba Rashid, Manahil Riaz, Misha Salam Bajwa, Aamina Jamil and Muhammad Touseef Khalid	134
22.	Epidemiology of Influenza Viruses …………………………………… Mehroz Latif, Muhammad Umar Hayat, Muhammad Hassan Rehman, Muhammad Irfan Anwar, Sehrish Gul, Mehvish Parveen, Namra Mariam and Muhammad Dania	143
23.	Impact of Food-Borne Diseases in Association to One Health Concept and Efforts of their Prevention …………………………………… Jwaria Shakeel, Taqveem Khalil, Maham Khalil, Nimra Shakeel, Rizwan Shukat, Muhammad Tahir Aleem, Irfan Shaukat , Aftab Shaukat, Rida Asrar, Hamza Sharafat	150
24.	Bacteriophage Therapy: Effective Antibiotic Replacer Against Emerging Ghost of Antimicrobial Resistant Bacteria …………………………………… Tariq Jamil, Ayesha Mehmood, Muhammad Haris Raza Farhan, Fakiha Kalim, Fazle Hadi, Khadija Younas, Qamar Iqbal, Rida Asrar and Ahmad Nawaz	158

25.	Strategies and Advancements for Control of Vector Borne Diseases of Public Health Concern .... Zurisha Rani, Asghar Abbas, Zohaib Saeed, Hafiza Amna Zaheer and Rao Zahid Abbas	168
26.	Detection of Emerging Zoonotic Pathogens: An Integrated One Health Approach .... Momna Mehmood, Muhammad Naeem Faisal, Muhammad Abdullah, Aiza Kamal Khan, Wania Nasir, Usman Haider, Najeeb Ullah Khan and Aneela Gul	175
27.	Sustainable Goals for Achieving Disease Control in Livestock and Animal Industry .... Muhammad Asad, Saima Qadeer, Asma Ashraf, Sana Ullah, Ammara Riaz, Kashif Ali and Sana Kausar	182
28.	The Use of Viral Vectors in the Treatment of Diseases (Viral Vectors for Gene Therapy) .... Azam Mokhtari and Mohamad Javad Ataie	190
29.	Social Awareness, the Main Dare for Environmental Health .... Miguel Ángel Karam Calderón, Shadye Matar Khalil, Gauddy Lizeth Manzanares-Leal, Yazmín Castillo Sánchez, Pablo Antonio Moreno-Pérez, Ninfa Ramírez-Durán	196
30.	Emerging Infectious Diseases in Perspective to Climatic Conditions .... Muhammad Bilal, Muhammad Kashif Saleemi, Aisha Khatoon, Muhammad Imran Arshad, Muhammad Imran and Shafia Tehseen Gul	201
31.	Conservation Medicine and Biodiversity in Iraq .... Rana M Al-Obaidi, Ridha Hasan Hussein, Ahmed Sami Shaker, Questan Ali Ameen, Korsh Ararat, Zaid Kh. Khidhir, Sehand K Arif and Israa Hameed Abd Al-Sada	209
32.	A Mutually Beneficial and Dynamic Relationship between Human and Animals .... Hawzhin Jamal Mahmood, Hadia Karim Zorab, Sazan Qadir Amin, Hana Hassan Mustafa	220
33.	Plastics and Microbiome: Impacts and Solutions .... Sara Omer Swar	228

1

Climate Change and Its Role in the Emergence and Re-Emergence of Zoonotic Diseases that Increase the Risk of Future Pandemics

AUTHORS DETAIL

Virginia Guadalupe García-Rubio*, Juan José Ojeda-Carrasco, Enrique Espinosa-Ayala, Pedro Abel Hernández-García and Laura Dolores Rueda-Quiroz

Centro Universitario UAEM Amecameca, Universidad Autónoma del Estado de México, México.
*Corresponding author: vggarciar@uaemex.mx

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INTRODUCTION

The current world scenario stands out for its complexity and uncertainty. The activities and processes tend to promote "social progress" as a way of gradual and generalized development and have marked an unprecedented footprint due to the significant deterioration produced on the planet (Hermi 2021).

Climate Change associated with greenhouse gas (GHG) emissions, generated mainly by the burning of fossil fuels for energy production, the development of industrial processes, the generation of waste and the unsustainable production of food and have modified the earth's atmosphere drastically. The manifestation of its effects is not only reflected in the increase in global temperature, but also in the recurrence of extreme weather events such as floods, droughts, tsunamis, torrential rains and heat waves affecting populations in the different regions of the world (Grubb et al. 2022; PAHO/WHO 2022).

Although the greenhouse effect is the most devastating indicator of climate change, the approach to this phenomenon as a process highlights the double interrelationship with respect to environmental deterioration. The increase in temperature and the meteorological events associated with climate change are altering the ecosystems; and the anthropogenic activities such as overexploitation, unsustainable use and pollution of natural resources, contribute to exacerbating the effects of this phenomenon (De La Rocque et al. 2008; Grubb et al. 2022).

The result is that the changing conditions in disturbed habitats put the resilience of many species to the test, accentuating migration and colonization of new niches, fragmentation and in the worst case, the loss of biodiversity, due to the effect on biocenoses, generating great imbalances in nature (Wilkinson 2018).

These imbalances are the result of the convergence and interaction of various factors associated with climate change and environmental deterioration, which negatively affect habitats, ecosystems and the dynamics of plant, animal and human populations (Gottdenker et al. 2014; IPBES 2019).

In contrast, these factors are contributing to increase the resistance of pathogens, the diversification of their reservoirs and vectors, as well as their dispersion. These new conditions are increasing the emergence and re-emergence of diseases that affect animal and human health, which is why they are assigned a relevant role in future pandemics, due to the zoonotic nature of many of them (Randolph et al. 2020).

The root of above-mentioned problems and their solution lies in the interaction of climate change with the emergence and re-emergence of zoonotic pathogens leading to a risk for future pandemics (Bebber 2015; Díaz and Cruz 2017). This recognition highlights the need to overcome partial and fragmented visions, aimed at reducing GHG emissions associated with climate change, promoting the sustainable use of resources to curb environmental deterioration, and addressing the health problems in a particular way (Khan 2018; Sánchez et al. 2022).

The "*One Health*" approach offers the alternative of a comprehensive approach, to generate criteria of understanding and approximation referenced and consistent with the current context (Khan 2018). The knowledge generated from this approach provides the necessary elements to assess the nature of the risk in which the planet finds itself. From this approach, the interrelationship established between environmental problems, threats and the levels of vulnerability of populations is the basis for the development of guidelines that simultaneously address environmental, animal, and human health (AFD 2020).

Climate Change and Environmental Deterioration

Climate change and environmental deterioration are the two determining factors of environmental Health (De La Rocque et al. 2008).

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Throughout history natural processes such as the friction of tectonic plates, volcanic eruptions, ocean currents, the magnetic field radiation and solar wind or the impact of meteorites, continuously modify the conditions of the planet. However, climate variability associated with human activities has a more significant impact (Grubb et al. 2022).

While natural processes have configured the earth's surface and contributed to the atmospheric conditions that allow the development of life on the planet, anthropogenic variability produces the opposite effects, due to the levels and intensities of its scope and effects (Wilkinson 2018; IPBES 2019).

According to the Intergovernmental Panel on Climate Change (IPCC), the measures adopted to reduce GHG emissions have proven ineffective at current levels. According to the experts, a 1.5°C increase in the planet's temperature in the next two decades is an inevitable fact, and there is even the possibility of exceeding this estimate, given the current behavior of emissions (Grubb et al. 2022).

This means that the risks linked to climate change may be exacerbated and its effects potentially more dangerous and devastating (Lee 2017). The evidence is convincing due to the increase in the incidence of natural phenomena (gravel avalanches, liquefaction, expansive soils, submarine landslides, volcanic eruptions) that are manifesting at a global level, which are affecting the productivity, health, safety and life of populations.

Additionally, human overexploitation of natural resources exerts a multiplier effect due to the disturbance and deterioration of natural habitats caused by changes in land use. This disturbance is associated with excessive logging, the expansion of crop areas or the raising of livestock, the development of infrastructure and the unsustainable use of resources, including the hunting of wild animals for human consumption, as a food alternative for the most vulnerable communities (Wilkinson 2018).

The sum of the effects of climate change and environmental deterioration, in addition to altering the essential life processes of organisms, increase competition for resources and territories, their vulnerabilities and the loss of biodiversity in ecosystems (Lorenzo et al. 2017; Sánchez et al. 2022).

Loss of Biodiversity, Emergence and Re-emergence of Diseases

One of the most significant consequences of climate change and environmental deterioration is the loss of biodiversity, which affects both the number of species of fauna and flora, and the structural composition of natural habitats. The consequences for human beings are diverse including increased air pollution, damage to the production of food and raw materials, increased vulnerability due to the recurrence of natural disasters, scarcity of drinking water, and particularly, the intensification of emerging and re-emerging diseases (Woolhouse et al. 2005).

The increase in environmental temperature caused by climate change offers favorable conditions for disease-transmitting vectors to increase their populations and modify their population dynamics, but also for pathogens to increase their replication rates, establishing themselves successfully in the new ecological environments (De La Rocque et al. 2008).

The loss of biodiversity caused by anthropogenic disturbances to ecosystems contributes to increasing the risk that humans will contract new diseases, many of these still unknown because these have wild animals as reservoirs. This is because the fragmentation of habitats reduces the richness of species and affects the means of human survival, especially in those communities that depend on hunting to cover their food needs (Wilkinson 2018).

The consequence is that by decreasing biodiversity, exposure to new pathogens increases and the incidence of diseases increases. Despite the fact that for years the feasibility of inter-specific transfer of pathogens was questioned, the increase in emerging diseases, especially zoonoses originating in wildlife and transmitted to humans, shows that not only environments have changed, but also pathogens are developing with greater capacities and resistance (Sánchez et al. 2022).

In addition to the proximity to natural reservoirs, the different routes of transmission tend to increase the risk for the establishment of zoonoses. Woolhouse et al. (2005), compiled bibliographic reports on pathogens that cause diseases in humans, identifying 1,407 different species. They found the following distribution: 208 species were viruses or prions (14.78%), (208 species), 538 bacteria (38.24%), 317 fungi (22.53%), 57 protozoa (4.05%) and 287 helminths (20.4%). Of the total, 816 (58%) were considered zoonotic species, 117 of which (12.58%) were in the category of emerging or re-emerging, with the highest percentage 13% (77 species) corresponding to viruses and prions, followed by bacteria 10% (54 species), fungi 25% (14 species), protozoa 25% (14 species) and helminths 3% (10 species). From the analysis of the data, they observed that the pathogens associated with zoonoses are twice as likely to be located within this category (emerging or re-emerging), than those that are not zoonotic.

Unsustainable agricultural production processes and changes in land use, to meet the demand for food and the housing needs of the populations, are altering the conditions in the ecosystems, which favor the development of pathogens and with it, of diseases (Cabello and Cabello 2008).

The level of impact that diseases can have will depend on the ability of pathogens to reproduce and diversify their hosts, the number of pathogens introduced into the population, the dynamics of the disease and the routes of transmission or contagion. Depending on the degree of involvement, they can manifest as territorially localized infections, epidemics or pandemics (Lorenzo et al. 2017; Randolph et al. 2020).

In recent decades, various contributions have highlighted and warned about the consequences of environmental deterioration for human and animal health. Prior to the

COVID-19 pandemic, in 2016 the United Nations Environment Program (UNEP) and the International Livestock Research Institute (ILRI) warned of the alarming increase in zoonotic epidemics. These organizations estimate that 60% of infectious diseases in humans have an animal origin and that around 75% of all new and emerging diseases, transmissible between animal species and ultimately to human highlight the close relationship between these diseases and the health of ecosystems (Randolph et al. 2020).

The maintenance of biodiversity in an ecosystem reduces the prevalence of pathogens and the risk of zoonoses. Therefore, the loss, fragmentation and deterioration of ecosystems, which are being decisive in the decrease and disappearance of species, in addition to altering the composition and dynamics of ecosystems, affects the relationships between animal populations and pathogens, increasing the risk of zoonoses and future pandemics (Woolhouse et al 2005; Wilkinson 2018).

The establishment of protected natural areas, the reduction of wildlife trade and changes in land use, as well as the sustainable use of natural resources can help reduce this problem. This underlines the importance of reestablishing environmental balances as a necessary condition for animal and human health (Wilkinson 2018; IPBES 2019).

Climate Change, Pathogens and Natural Reservoirs

Although the evidence of many experts tends to highlight the growing capacity to prevent future pandemics, the truth is that the ways in which this problem is addressed still present areas of opportunity. This is so, because the trend followed until now is to generate responses to the diseases that appear, rather than directing efforts towards their prevention (Losa 2021).

Much of the current problem is associated with environmental changes caused by anthropogenic activities. According to the Intergovernmental Platform on Biodiversity and Ecosystem Services (IPBES), the change generated in the environment in the last fifty years is unprecedented. The irrational use of the land and sea, the over-exploitation of wildlife, pollution and climate change, associated with human activities of production and consumption, are affecting the health and subsistence of many communities in different regions of the world (IPBES 2019).

Epidemics and pandemics such as the black and bubonic plagues, smallpox, the Kansas, Russian, Asian, Hong Kong and Spanish flues, cholera and HIV have been part of the history of humanity, affecting many generations due to the multiplicity of infections, high mortality rates and the economic and social costs. However, the living conditions of the current globalized world break with the historical trend due to the frequency, diversity and prevalence of diseases that affect animal and human health (Sánchez et al. 2022).

The alterations to the natural ecosystems, the continuous human mobilizations between zones and regions of the world, the exports and imports of food, supplies and products of animal origin, have caused these epidemics, in addition to diversifying, to have greater scope both in their effects and in their spatial distribution (Morens and Fauci 2020). Bovine spongiform encephalitis, avian, swine and H1N1 influenza, Severe Acute Respiratory Syndrome (SARS) and recently monkey pox are clear examples that the recurrence of diseases is changing rapidly (WOAH 2021).

The World Organization for Animal Health recognizes that 60% of pathogens that affect human health come from wild and domestic animals and that 75% of emerging human pathogens have an animal origin (WOAH 2021). Experts in the study of epidemics and pandemics agree that around 70% correspond to zoonotic diseases (PAHO/WHO 2021).

This irrefutable fact draws attention to the ways of contagion of these zoonoses, whether by direct contact with infected animals, the consumption of food from infected animals, both meat and its derivatives, contaminated water, and the aerial dispersion of pathogens (sprays) (Randolph et al. 2020).

The animal-human interrelation that is established in zoonoses represents a complex plot delineated by the convergence of a diversity of factors, whose backdrop is the disturbance to ecosystems produced by human beings and amplified by the effects of climate change, generating dissimilar conditions to those existing decades ago. The increase in contact between wild animals, with peridomestic and domestic animals, extensive livestock farming, the loss of biodiversity and the growing resistance of pathogens, establishes new dynamics in this interrelation (Vega 2019).

The increase in environmental temperature caused by climate change favors the expansion of pathogens and their vectors and increases the risk that diseases that have been eradicated or kept under control will re-emerge or assume new dimensions; but also, that others such as COVID-19 unknown until now, begin to express themselves (Díaz and Cruz 2017).

The temperature and extreme manifestations of climate change are exacerbating the damage to ecosystems caused by human activities, affecting the biotic interactions that are established between flora, fauna, microorganisms, vectors, reservoirs and the human being, which is modifying progressively the incidence, prevalence and distribution of diseases that affect human and animal health (Díaz and Cruz 2017; Lorenzo et al. 2017).

Although the damage produced by the proliferation of pathogens in plants is not directly related to zoonoses, the alterations caused by changes in temperature, abnormal rainfall patterns, droughts, erosion and organic impoverishment of the soil are environmental factors that increase the number of vectors and pathogens that affect plants. There are modifications in their physiology, resistance and biomass production, negatively affecting both food chains (mainly herbivores) and the availability of food for animals and humans (Bebber 2015).

In addition to the effects on the cycles and productivity of plants, climate change is having strong influences and determinations in the pathogen-animal-human being interface. Particularly in pathogens, it is favoring the amplification of their reproductive capacities, mutation, expansion, colonization in multiple hosts and resistance, which is especially important in the emergence and re-emergence of diseases and zoonoses (Gottdenker et al. 2014).

With the deterioration of natural habitats and the reduction of available resources, wild animals face greater inter- and intra-specific competition, increased migrations that modify their ecological niches, decrease or disappearance of some species and changes in susceptibility to develop diseases (Olival et al. 2017).

These modifications are outlining new scenarios, not only due to the loss of species linked to biodiversity, but also because many of the species that are disappearing were the natural reservoirs of pathogens that under this circumstance colonize other hosts. This is of special importance, because one of the conditions for the persistence of a zoonosis in a certain geographical area is the maintenance of wild reservoirs, a condition that in the current climatic-environmental conditions is favored by the capacities of the pathogens, as well as the vulnerability of the animals (Lorenzo et al. 2017).

Although in nature, pathogens have a large number of microscopic and macroscopic organisms as intermediate hosts, in zoonoses, the relevance falls on vertebrate reservoirs, with which the development of diseases in humans is associated. According to the etiological or causal agents, these diseases can be bacterial (for instance, leptospirosis, brucellosis, campylobacteriosis, anthrax, tuberculosis), viral (hemorrhagic fevers -dengue, zika, chikungunya-, rabies) and parasitic (Chagas disease, hydatidosis, diphyllobothriasis) (Cabello and Cabello 2008; Lorenzo et al. 2017).

The reservoirs of zoonoses can be fish, amphibians, reptiles, birds and mammals. In the first three groups, transmission is generally horizontal, through water or soil, meat consumption, contact with infected animals, and in the case of reptiles through direct contact, wounds, scratches or other injuries, that has proliferated due to the capture of animals as pets, although they occur in smaller proportions, considering the total number of zoonoses (Vega 2019).

In the case of birds, only a small number of the viruses that affect them can be transmitted to humans, due to evolutionary divergence (which would imply the jump of pathogens not between species, but between classes), physiological and the mechanisms of innate immunity of birds. Among those that develop as zoonoses, such as Flaviviruses or encephalitic viruses (arboviruses), arbozoonoses and influenza or avian influenza (which is transmitted by air), the latter has had a significant impact on the health of human beings and food security, due to the thousands of birds that are slaughtered for having contracted the virus (Jiménez-Clavero 2014).

Of the wild fauna, mammals have a relevant position in terms of zoonoses, due to the species involved as reservoirs, the diversity of pathogens they harbor, the role they are having in the maintenance, transmission and dispersion of zoonotic agents, and therefore, in the emergence and re-emergence of diseases (Hermida-Barroto et al. 2022).

The alterations that accompany climate change and the deterioration of ecosystems are defining scenarios in which biological and ecological factors are changing the reservoir-pathogen-disease relationship and increasing the risk of future pandemics at an alarming level (Randolph et al. 2020).

The importance given to mammals is associated with the fact that the vast majority of emerging zoonotic diseases, such as SARS, HIV, Ebola and COVID-19, originated from wild mammals (Díaz and Cruz 2017).

I+n addition to biodiversity loss, human encroachment on natural habitats is generating greater exposure to wild species, which until now remained natural reservoirs of pathogens (enzootic cycles), without causing diseases in humans (Olival et al. 2017).

With the loss of species, the dynamic populations are affected. Of all the bio-relationships present in ecosystems, the loss of predators is promoting an increase in rodent populations, a reservoir for a significant number of pathogens associated with zoonoses, but also the development of diseases in domestic animals, which have closer proximity to humans (Llanos-Soto et al. 2019). Of the zoonotic reservoirs of wild animals, rodents and bats are served as a major reservoir to transmit the infection (Ruiz et al. 2010).

Wild rodents, in addition to playing an active role in the circulation of pathogens in endemic foci, also play an active role in the dissemination of pathogens in rural areas. When commensal rodents in these areas are exposed to wild rodents, they can become infected directly (urine, feces and other infected excretions) or indirectly through vectors (fleabites, lice, mosquitoes, insect bites or ticks), increasing the risk to the health of humans and domestic animals (Vega 2019).

The zoonotic diseases in which rodents participate include bacterial (Leptospirosis, Tularemia, relapsing fever, brucellosis, among others), rickettsial (weed typhus, murine typhus, Rocky Mountain spotted fever), viral (Choriomeningitis, pulmonary and renal hemorrhagic, equine encephalitis), parasitic (Trichinosis, Schistosomiasis, Hymenolepiasis) and protozoal diseases (Leishmaniosis, Chagas disease, Toxoplasmosis, Giardiasis, Trypanosomiasis) (Torres-Castro 2017).

For their part, bats play an important role in the spread of viral zoonoses. Olival et al. (2017), in an investigation analyzed virus-host relationships and found that bats are the mammals that harbor a greater proportion of zoonotic viruses, transmissible both to humans and to others animals.

Despite the fact that the number of bat species is equivalent to about 50% of rodent species, they proportionally exceed 30% of the pathogens for which they function as reservoirs. The viruses that cause the Ebola zoonoses, Severe Acute Respiratory Syndrome (SARS-CoV-1) and Middle East Respiratory Syndrome (MERS-CoV), have their origin in bats (Hermida-Barroto et al. 2022). Most epidemiologists agree that viral zoonoses associated with bats, rather than being transmitted to humans through direct contact with reservoirs, occur through contact with intermediate hosts, or through contamination of agricultural areas with bat-infected guano and urine (Morens and Fauci 2020).

Although among all wild animal species, rodents and bats are highly relevant, other species that are natural reservoirs also participate in infectious processes. Migration fueled by climate change and human disturbance of natural habitats is closing the proximity between wild and domestic species (Randolph et al. 2020).

The increase in contact with wild animals is increasing exposure to pathogens and with it, the number and diversity of diseases that affect the health of animals and humans in an alarming way, making the interactions between these agents increasingly complex (Vega 2019; Sánchez et al. 2022).

The conditions associated with climate change are influencing the spatio-temporal distribution and the seasonal and population dynamics of pathogens, vectors, reservoirs and hosts (Rodríguez et al. 2013). These circumstances, in addition to outlining a new reality, are being decisive in three aspects that, from the epidemiological point of view, are fundamental: the pathogens themselves, their reservoirs/vectors/hosts, and the transmission mechanisms (PAHO/WHO 2021; WOAH 2021).

New reality: New Ways of Approaching the Study of Diseases

Despite the large number of contributions generated around pathogens and the diseases they produce, the current problem outlines a reality that shows the need to generate new ways of approaching the study of diseases, which provide the possibility of influencing their prevention, rather than care once, they have manifested (Sánchez et al. 2022).

The most recent current benchmark, the COVID-19 (SARS-CoV2) pandemic, is a clear example that traditional pathogen study systems have been overwhelmed. The most recent figures show the great impact that it has caused: a little more than 548 million infected and more than 6.3 million deaths, with an affectation in practically all the countries of the world, including the insular ones such as Greenland, Iceland, Madagascar, the Fiji Islands, the Philippines, Cuba and the Dominican Republic. A little over two years later, various studies on the coronavirus have provided knowledge about the coronavirus and its variants, but until now its origin is still not specified, although there is a great coincidence that the virus came from bats (PAHO/WHO 2022).

The need to generate new forms of approach is due to the approach historically used, where when studying the pathogen-host relationship, the circumstances and effects they have on the hosts are privileged, and not the aspects related to pathogens, such as their origin, interrelationships and forms of transmission (Morens and Fauci 2020).

The complexity of the interactions, influenced by climate change and biodiversity loss, highlights the importance of studying this relationship by addressing the pathogen first, in order to manage zoonotic diseases more effectively and efficiently (CEPAL et al. 2021).

The new form of approach outlined recently, the *Stockholm Paradigm*, proposed by Brooks et al. (2019), raises the possibility of better understanding the pathogen-host interrelationships from their own complexity. From this perspective, a better understanding of the nature of the pathogen will make it possible to understand the development of its capacities, both to exploit a greater number of viable hosts, and to transcend to other physical spaces where they can locate new hosts that were not previously present exposed, but are susceptible.

To understand the complexity of pathogen-host interactions, from this paradigm the key lies not in seeking to understand the particular ways in which each pathogen develops in a given environment, but in how they acquire the ability to take advantage of new opportunities with respect to hosts. This is a function of the ecological adjustments that are produced both by climate change and by the destruction of ecosystems generated by human activities (Brooks et al. 2019).

From the authors' point of view, variations in host ranges may be due to alterations in the trophic structure, the entry of susceptible hosts into the ecosystem, the geographic expansion of the pathogen, or the development of new adaptive capacities of the pathogens. However, neither of these circumstances correlates with host range or diversification rates. Rather, they reflect the opportunities that pathogens have for the establishment of new associations, either through greater access to natural hosts that were not previously susceptible or contact with species introduced to the ecosystem, both introduced (domestic) and wild species that they reach the ecosystem by migration (Basco 2018).

As stated, in order to understand the pathogen-host relationship, rather than addressing the particular study of pathogens and/or hosts, it is necessary to understand that, as they are complex systems, their generalities cannot be associated with emergent properties, such as the interactions between the pathogens and their hosts, or associated diseases. Rather, it is necessary to modify the approach criteria around pathogens, diseases and the changes that are occurring in the contexts in which they develop. For this purpose, it is necessary to direct studies to the ecology of pathogens and the contexts in which they establish interactions with hosts, which will allow us to understand the difficulties that a pathogen goes through to establish itself in a given host, but also, the propagation facilities that it has once it achieves it. That is, those pathogens that infect easily but spread slowly in wild species can rarely infect domestic animals and humans; but when they do, they spread rapidly, spawning epidemics and pandemics (Uribe 2015).

A crucial element of this paradigm is to consider that pathogens have extensive colonizing capacities, many of which are only expressed when changes in the environment make it possible, which is reflected in the increased prevalence of both emerging and re-emerging diseases, affecting plants, animals and humans. The expansion towards other hosts occurs as a response to changes in the dynamics of ecosystems, either due to the effect of manifestations of climate change, disturbance, invasion and irrational use of natural resources caused by human activities. Likewise, due to the modification in the composition of the species that inhabit a certain biotope, associated with the loss of biodiversity, the action of invasive species or the introduction of domestic animals, by expanding the breeding and grazing areas, in forests. From this paradigm, this implies that pathogens have inherent capabilities, refuting the idea that they are "rapidly evolving" to colonize a larger number of hosts. It is the current environmental conditions, and the effects on the communities of plants, animals, and even humans, that are leading to increased opportunities for pathogens to broaden the spectrum of hosts. As long as the environmental damage continues, exacerbated by climate change, the opportunities for pathogens to continue producing diseases will expand (Brooks et al. 2019).

The approach to the nature of pathogens from this paradigm allows us to understand that the capacities they express depend on the occurrence of specific characters of the hosts, which represent potential opportunities for pathogens to expand their colonization. Under current conditions, the breakdown of balances in ecosystems caused by climate change and environmental deterioration is significantly violating natural containment barriers, favoring the expansion of colonization of hosts by pathogens. From this consideration, if alternatives are not implemented that seek to mitigate the effects of climate change, as well as the anthropogenic damage produced to ecosystems, the number and diversity of diseases will increase, as well as the degrees of affectation that they produce in the plant, animal and human health (Uribe 2015; Basco 2018).

The “One Health” Approach as a Comprehensive Alternative to Zoonoses

The emergence and re-emergence of manifest diseases in recent years are a reflection of the interactions between the environment, pathogens and human beings (Gottdenker et al. 2014). The impact on the environment comes from the serious alterations and imbalances generated in ecosystems and their biodiversity, due to human activity and exacerbated by the progressive advance of climate change (Bebber 2015). These conditions favor the expression of the inherent capacities of pathogens (mainly viruses), associated with their evolutionary biology and genetic diversity, to broaden their host spectrum. As for the vulnerability and susceptibility of animals and humans to contract diseases, it outlines an uncertain panorama for present and future generations (Morens and Fauci 2020).

This irrefutable scenario forces us to modify not only the way in which pathogens are studied, but also the way in which we are reacting to diseases that are affecting health. The implementation of strategies that simultaneously integrate environmental, human and animal health is required (AFD 2020).

Protecting ecosystems and the diversity of species will allow the reestablishment of environmental balance, reduce the spread of pathogens and thereby prevent, as far as possible, the development of future diseases. In recent years, the “One Health” approach represents a potential means for the management and prevention of zoonoses, offering the possibility of comprehensively addressing environmental, animal, and human health (Khan 2018).

Building on this approach is seeking to reduce the health risks currently faced. On average, of every five newly emerging diseases, three are zoonotic. To address the goal of significantly reducing disease emergence, the key element of this approach is to recognize the interdependence that exists between human, animal, and ecosystem health. Addressing this interdependence, therefore, requires collaborative and multidisciplinary work, from various specialists who converge on the objective of restoring health on the planet, in the three aspects indicated. Since 2010, the three international intergovernmental organizations that are coordinating efforts to advance the “One Health” approach are the World Health Organization (WHO), the World Organization for Animal Health (OIE) and the United Nations for Food and Agriculture (FAO) (Randolph et al. 2020).

As part of this tripartite alliance, the OIE recognizes the fundamental role that Veterinary Services have in promoting and protecting the welfare and health of animals. Ensuring animal health will reduce the incidence of zoonoses in humans, while contributing to food security by controlling the conditions for raising livestock and guaranteeing the availability and safety of food of animal origin (AFD 2020).

Despite being a relatively recent approach, since 2017 various collaboration networks have been promoting intersectoral participation. Although some of them focus their attention on animal and human health care, leaving aside the environment (Khan 2018), the One Health approach begins to spread throughout the world, involving the multidisciplinary work of scientists and academics, government agencies, non-governmental organizations and private initiative, interested in addressing this problem (Sánchez et al. 2022).

This approach seeks to overcome the anthropocentric vision of evaluating the risks of pathogen transmission only through the effects on human health (AFD 2020).

Understanding that animal health is also suffering the ravages, both in direct correlation due to the deterioration caused in the environment, allows us to recognize the necessary transversality that must exist to generate a greater understanding to face the global health risks associated with zoonoses (Sánchez et al. 2022).

From this transversality, it seeks to promote the development of new skills and ways of approaching current health problems. The objective is to assess the advances generated so far regarding pathogens and their hosts, to identify new directions to develop, in accordance with current contextual conditions. The ultimate goal is to build the conditions of possibility to implement remediation strategies, based on the simultaneous improvement of human, animal and ecosystem health, as a measure to prevent the emergence of new pandemics (AFD 2020; Randolph et al. 2020).

Conclusion

The magnitude of the current environmental problem reveals a new reality. Various factors associated with climate change and environmental deterioration negatively impact natural habitats and ecosystems. The fragmentation of habitats reduces the richness of species causing loss of biodiversity, with which the risk of disease development increases by favoring the dispersion and resistance of pathogens and the diversification of their reservoirs and vectors. These conditions are determining factors in the increase in the emergence and re-emergence of diseases, with great effects on the health of animal and human populations. The "One Health" Approach offers the necessary elements not only to assess the nature of the risk facing by the planet, but also to implement remedial measures that allow overcoming the current problem where infectious outbreaks can produce different degrees of affectation in the form of territorially localized infections, epidemics or pandemics.

REFERENCES

AFD, 2020. Frente a las pandemias, One Health: Un enfoque integrador de la salud humana, animal y ambiental. Agence Française de Développement.

Basco AI, 2018. Medio Ambiente y Cambio Climático. BID (Banco Interamericano de Desarrollo).

Bebber DP, 2015. Range-expanding pests and pathogens in a warming world. Annual Review of Phytopathology 53: 335-356.

Brooks DR et al., 2019. The Stockholm Paradigm. Climate Change and Emerging Disease. University of Chicago Press; pp: 400.

Cabello CC and F Cabello, 2008. Zoonosis con reservorios silvestres: Amenazas a la salud pública y a la economía. Revista Médica de Chile 136(3): 385-393.

CEPAL et al., 2021. Salud y Cambio Climático: Metodologías y Políticas Públicas. Comisión Económica para América Latina y El Caribe, Ciudad de México; pp: 129.

Grubb M et al., 2022. AR6-Mitigation of Climate Change. Intergovernmental Panel on Climate Change-IPCC.

Gottdenker NL et al., 2014. Anthropogenic Land Use Change and Infectious Diseases: A Review of the Evidence. EcoHealth 11(4): 619-632.

De La Rocque S et al., 2008. Climate change: impact on the epidemiology and control of animal diseases. Revue Scientifique et Technique 27(2): 303-308.

Díaz SP and Cruz SM, 2017. Cambio climático: efecto sobre la reemergencia de enfermedades infecciosas y parasitarias, REDVET. Revista Electrónica de Veterinaria 18(9): 1-13.

Hermi ZM, 2021. Cambio climático antropogénico y decrecimiento. Ar@cne: Revista Electrónica de Recursos en Internet sobre Geografía y Ciencias Sociales, Vol. XXV, Núm. 250: 1-30.

Hermida-Barroto MC et al., 2022. El murciélago como fuente de zoonosis virales. MEDICIEGO. Revista Médica Electrónica de Ciego de Ávila 28: e1941.

IPBES, 2019. The Global Assessment Report on Biodiversity and Ecosystem Services. Platform on Biodiversity and Ecosystem Services. Intergovernmental Platform on Biodiversity and Ecosystem Services.

Jiménez-Clavero MA, 2014. Las aves como reservorio de virus zoonóticos. Virología 17(1): 54-62.

Khan MS, 2018. The growth and strategic functioning of One Health networks: a systematic analysis. The Lancet Planetary Health 2(6): 264-273.

Lee AA, 2017. Climate change is one of the world's greatest risks. Inter-American Development Bank. Release January 31, 2017.

Llanos-Soto S et al., 2019. Conocimiento acerca de los patógenos virales y bacterianos presentes en mamíferos silvestres en Chile: una revisión sistemática, Revista Chilena de Infectología 36(1): 43-67.

Lorenzo MC et al., 2017. Enfermedades zoonóticas virales emergentes. Importancia ecológica y su evaluación en el sureste de México. Sociedad y Ambiente 5(15): 131-146.

Losa GJE, 2021. Enfermedades infecciosas emergentes: una realidad asistencial. Anales del Sistema Sanitario de Navarra 44(2): 147-151.

Morens DM and AS Fauci, 2020. Emerging Pandemic Diseases: How we got to COVID-19. Cell Press 182: 1077-1092.

Olival KJ et al., 2017. Host and viral traits predict zoonotic spillover from mammals. Nature 546: 646–650.

PAHO/WHO, 2021. Zoonoses. Pan American Health Organization, World Health Organization.

PAHO/WHO, 2022. COVID-19 Situation Reports. Accessed August 2, 2022. Pan American Health Organization, World Health Organization.

Randolph DG et al., 2020. Preventing the Next Pandemic: Zoonotic diseases and how to break the chain of transmission. United Nations Environment Programme and International Livestock Research Institute Nairobi, Kenya.

Rodríguez DJG et al., 2013. Climate changes and their effect on some groups of parasites. Revista de Salud Animal, Vol. 35, No. 3: 145-150.

Ruiz PHA et al., 2010. Mamíferos silvestres y sus patógenos zoonóticos. Biodiversidad y Desarrollo Humano en Yucatán, CICY, PPD-FMAM, CONABIO, SEDUMA, México; pp: 496.

Torres-Castro MA, 2017. ¿Son los roedores sinantrópicos una amenaza para la salud pública de Yucatán? Revista Biomédica 28(3): 179-186.

Sánchez A et al., 2022. In the beginning, it was zoonosis: One Health to combat this and future pandemics. SESPAS Report 2022. Gaceta Sanitaria 36(1): 61-67.

Uribe BE, 2015. El cambio climático y sus efectos en la biodiversidad en América Latina, CEPAL; pp: 86.

Vega ARL, 2019. Zoonosis emergentes y reemergentes y principios básicos de control de zoonosis. Revista de Medicina Veterinaria 17: 85-97.

Wilkinson DA, 2018. Habitat fragmentation, biodiversity loss and the risk of novel infectious disease emergence. Journal of the Royal Society Interface 15: 20180403.

WOAH, 2021. Global health risks and tomorrow's challenges. World Organization for Animal Health.

Woolhouse ME et al., 2005. Host range and emerging and reemerging pathogens. Emerging Infectious Diseases 11(12): 1842-1847.

2

Impact of Climate Change on Animal Health

AUTHORS DETAIL

Sayyed Aun Muhammad*[1], Abdul Rauf[1], Hamza Ali[1] and Muhammad Awais[1]

College of Veterinary and Animal Sciences Jhang 35200, Pakistan.
*Corresponding author: aun.muhammad@uvas.edu.pk

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INTRODUCTION

Climate change can be defined with respect to any domain of life like public health, animal health and food security. In fact, climate change is blend of changes resulting in natural phenomena and human activities that is limiting circle of feasibility in various ways and in various domains of life over a comparable longer period of time. Floods, droughts, earthquakes, deforestation, heavy or no rains, elevated temperature curve throughout the world, rise in greenhouse effect, relative risky values of air quality index and temperature humidity index, emerging issue of global warming, sudden and quick fluctuations in weather patterns and various other factors are contributing to insecure food chain, public health issues and adaptive behavior of livestock against the anticipation. It may have high alert status especially in poor countries near the equator. Increased infectious pathogenic microbial load, existence of multi drug resistant organisms, quantitively and qualitatively enhanced zoonotic threat, nutrition deficient food and many more are the outcomes of climatic change. Elevated prevalence of infectious diseases in animals like campylobacteriosis, mycosis, salmonellosis, helminthic infection and mange in different regions may be credited to climate changes with the passage of time. Keeping in view related factors responsible for change in climate and its impact on life demands livestock free of any kind of climatic abuse that will ultimately assure secure food chain, safe public health zone, pathogen free environment, well sustained and maintained ecosystems and animal welfare goals. It is need of the hour to highlight and address the worsening situations for animals due to rapidly changing climate (Ali et al. 2020). This chapter fulfils the demand and focuses on how the changing climate influences the lifestyle of animals and compels them to adapt in order to survive through the deviated changes in climate.

Heat Stress and Productivity of Animals

Animals respond to change in environment through adaptation and climate through acclimation and in fact both, adaptation and acclimation are defined as the ability to adjust according to evolution. The phenomenon by which animal responds to any unexpected worse condition is stress. Acclimation is commonly a concern of various generations. Usually, two terminologies have been used in literature, heat load that is harsh environmental conditions and heat stress that is how animal responds such situations. Heat stress to animals especially livestock i.e., poultry, sheep, goat, horses, cattle & buffalo, is usually graded as no stress, mild stress, moderate level stress and severe stress. Persistent exposure to severe heat stress is attributed as animal abuse and against the objectives of animal welfare. Animals that are frequently exposed to severe stress, usually show relatively weak body conditioning scores, weak immunity, less production and reproduction potential, less feed intake, more fluid loss (sensible or insensible) and loss of cognition. Representative concentration pathway (RCP) from 4.0 to 5.0 and temperature humidity index (THI) <80 is considered as normal limits for livestock management and growth. Regions with less RCP and THI show reduced saturation of livestock. Sheep and goats are relatively more prone to heat stress and thus, there is decrease in caprine and ovine farming trend in hot regions like in Africa (Camberlin 2017). Heat stress induces more sweating, more peripheral circulation, elevated body temperature, less urination, polypnea, recumbency, tachycardia, less digestion, less fermentation in rumen, less metabolism, and ultimately overall less performance in animals. Observation of more somatic cell count and less protein content in milk indicates more prevalence of mastitis in dairy animals facing heat stress. Expression of heat tolerant genes with the passage of time and altered metabolic profile are good acclimations but unfortunately, may accompany expression of genes with less production. Abortions have been reported due to heat stress affecting blastocyst formation and embryonic implantation in cattle and buffalo. This window of abortions has been narrowed down by modern techniques in reproduction like in vitro fertilization and embryo transfer. Detrimental effects of higher THI values on spermatogenesis are reported in literature and proved a hinderance in the collection and processing of semen and compromising the viability of sperms. Stress can be estimated by feces, plasma, blood and hair cortisol levels for per acute, subacute, acute and chronic conditions. Estimation of cortisol levels doesn't confirm that stress is from heat in fact any stress condition can elevate cortisollevel.

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Table 1: Temperature humidity Index of different countries and number of dairy cows suffering from heat stress

Country	Temperature Humidity Index (%) range observed in summer months	Number of dairy cows at risk
Australia	76-81	60,101
Caribbean	70-84	1,651
Mexico	73-82	22,71,42
Ukraine	59-70	1,700,000
Netherlands	60-81	6,033,922
Italy	76-81	316,160
Germany	53-76	25,143,828
Philippines	73-83	38,000
China	68-79	1,000,000
India	79-85	48,610,350
Zambia	72-89	3,700,000
Costa Rica	74-78	404,316
South Africa	72-87	13,700,000
Brazil	73-76	121,000,000

Infrared thermography is more accurate technique for determining heat stress in animals. Yearly rise of 1^{o}C in temperature curve of different regions has been recorded differently in the world including Africa that may be 2^{o}C in future i.e., after 2050, may prove a warning for livestock farming as well as wildlife leading to dominance of expression of less production genes that can be minimized by preferring local breeds and breeding of animals expressing heat tolerant and more production genes (Rahimi et al. 2021). Table 1 shows Temperature Humidity Index of different countries and number of dairy cows suffering from heat stress or going to suffer in future if THI management is not considered substantial in dairy industry.

Heat Stress and Metabolic Changes in Animals

Optimum metabolic profile in animals is discoverable in optimum environment that is different for different species and dependent on genetic potential of animals making them suitable and comfortable for different regions. Biological parameters that are optimum for some species may be less suitable for others. Global rise in temperature is limiting the utilization of oxygen, giving rise to hypoxic lifestyle and compromising overall potential of animals. This is a threat for swine, poultry and marine life due to heat stress imposed by huge fat content in subcutaneous tissue, thick coat of feathers inducing heat stress existence of algal blooms, microplastics and pollutants. Global change in temperature is transforming gut microbiota ubiquitously. Close association of gut microbes with genetic changes due to obesity and associated health disorders have been observed in animals (Vallianou et al. 2019). Fig. 1 depicts the prevalence of acidosis in different regions depending on the climate of that region.

Persistent exposure to heat stress has given rise to reduction in secretion of glucocorticoids, catecholamines, growth hormones and thyroids, imposing the issues of indigestion, lameness, hypoglycemia, liver dysfunction, clinical ketosis, hypoalbuminemia, hypocholesteremia, reduced metabolic rate and metabolic heat, compromised metabolism and failure in weight gain policies. Persistent fall in level of thyroid hormones and albumin indicate heat tolerance in farm animals. Panting, hyper salivation and ventilator activities in high temperature stress result in reduced blood carbon dioxide concentration and loss of bicarbonate ions in urine, triggering anaerobic mode and creating conditions of metabolic and ruminal acidosis that are reported majorly as subclinical disorders and respiratory alkalosis. Oxidative stress in animals round the world may be credited to acute heat stress provoking the environment with excess of free radicals, oxidation of lipids and proteins, tissue acidosis and cytotoxicity (Gonzalez-Rivas et al. 2020).

Change in Climate and Emerging Issue of Drug Resistance in Animals

Rise in demand of energy has led to vast commercialization of livestock sector globally. Commercialization has evidence of enhanced risk of infectious diseases as shifting of extensive systems to semi-intensive and intensive systems has led to increased prevalence of bacterial and viral diseases (Hayek 2022). After myocardial infarction, infectious diseases are second major cause of mortalities in humans as well as in animals. Mortality rate may touch 10 million/year by 2050 by resistant microbes if left neglected. This new tsunami of infections is usually combat by antibiotics. Use of antibiotics in livestock and public health touched the heights in previous two decades. Development of resistance in bacteria is natural but injudicious use of antibiotics, untreated slaughter house wastes, drug residues in animal products, ineffective routes of drug administration, under dosage of drugs, frequent use of same drug, negligence in spectrum of drug, lack of culture and molecular based approaches for diagnosis, over the counter access to antibiotics, lack of health literacy in patients, anthropogenic activities and rising temperature curve round the world-all are accelerating the process of antimicrobial resistance (AMR) (Fig. 2). Evolution of environment and increase in population has led to the presence of minerals like zinc, mercury, copper and compounds like herbicides

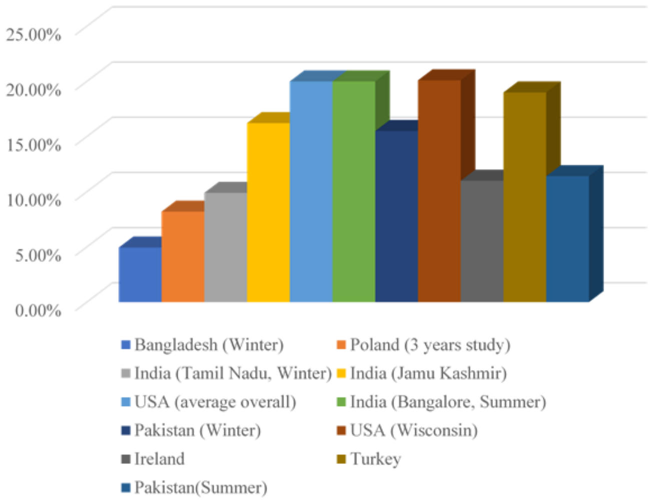

Fig. 1: Prevalence of subacute ruminal acidosis in dairy animals in different countries depending on the climate.

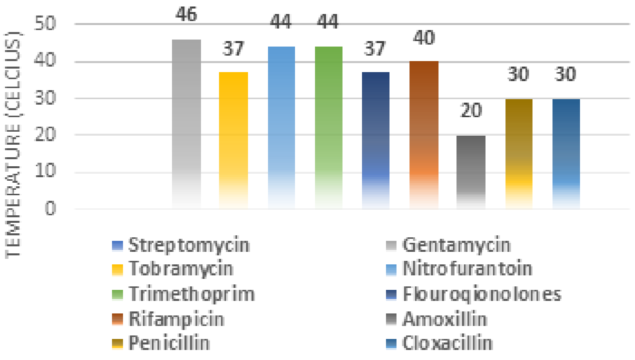

Fig. 2: Showing relationship between temperature and antimicrobial resistance (AMR) against given antibiotics where temperature has been plotted against vertical axis in Celsius.

and pesticides and resistant genes (Ahmad et al. 2021, Tian et al. 2021). Multi drug resistant Haemonchus species in sheep and goat throughout the world are imposing animal health issues and economic hurdles to livestock sector. About 14% of human population is said to possess Extended Spectrum Beta Lactamase (ESBL) genes predicting vast enteric cases in future like Campylobacteriosis and Salmonellosis that is a threat to animal health as well. Emergence of resistant genes is assisted by water bodies, high temperature humidity index, hot and cold shocks, open putrefaction of carcasses, aquaculture and anaerobic digestion. There are evidences of enhanced drug resistance with the rise in temperature due to effect on cell physiology. Three bacteria, *Klebsiella pneumoniae*, *Escherichia coli* and *Staphylococcus aureus* are currently under the umbrella of critical focus by FAO, OIE and WHO for veterinary as well as public health concerns and resistance has been reported after every 10°C rise in temperature of surroundings (Macfadden et al. 2018). Formation of biofilm against antibiotics e.g., in *Roseovarius* is believed to be formed at elevated temperature. Experimentally infected fish exhibit higher mortality when observed in higher temperatures even when supplied with antibiotics in aquaculture. Temperature induced mutations in Food and Mouth Disease (FMD) virus and Peste des petits for ruminant's virus (PPR) have been acknowledged globally. Rise in temperature enhances water holding capacity of particular area leading to precipitation, droughts, floods and heat stress that may result in resistant outbreaks in humans and animals and it may be through hyperactivity of vectors. If this relationship continues between temperature and AMR, it may open a door to post antibiotic era dominated by the use of new technologies in therapeutics like use of nano particles. It is injudicious to blame only increased temperature playing role in AMR as cold climatic shock also contributes in developing AMR by provoking resilience in DNA gyrases and creating hurdles in the way of fluoroquinolones. Presence of organic matter either on land or aquaculture causes accumulation of antibiotics contributing to depletion of their principles of action by pretherapeutic and ineffective exposure to microbes. Environmental pollutants like nitrogen wastes and carbon dioxide aid in AMR development as antibiotics have also been classified as environmental pollutants when used in excess. So, changes in climate in any form have a definite impact in the development of AMR that can't be restricted or limited but it's an emerging global challenge that direly needs to be addressed publicly (Ahmad et al. 2021).

Impact of Climatic Microplastics on Animal Health

Environmental pollution shows great diversity and microplastics is one of silent threat (Xiang et al. 2022). Use of plastics has increased exponentially in previous decade and it is expected to be three times by 2060 from 270 to 290 million tons worldwide. All these synthetic polymers are directly or indirectly being released into the environment due to lack of recycling facilities and awareness. Plastic compounds are degraded in the environment into smaller particles below the size of 5mm, called microplastics. 20 MP in 10g of human feces has been reported and this positive value may be credited to food from aquatic life as aquatic animals are more prone to microplastics (Huang et al. 2021). Although more than 600 aquatic species are suffering from microplastics yet the fishes are showing more alarming level due to direct dispose of industrial and agriculture wastes to aquatic bodies. Microplastics get accumulated in different body organs causing hepatotoxicity, gallbladder and pancreatic dysfunction, reduced body weight, reduced lipid content in body, inflammatory reactions, oxidative stress leading to apoptosis, mutations, gut associated problems, nephrotoxicity, and muscle deterioration (Huang et al. 2021). Microplastics affect all four barriers of gut i.e., physical, chemical, microbiological and immunological. Damaged intestinal barrier results in malabsorption, direct entrance of microbes into circulation through damaged goblet cells antigen specific pathways (GASP) and production of reactive oxygen species. Microplastics may induce goblet cells carcinoma and hypersecretory activity to goblet cells, compromised enzymatic activity of gut and acetylcholinesterase, maldistribution of gut microbiota and local inflammatory reactions leading to over secretions of inflammatory mediators (Huang et al. 2021, Wang et al. 2021) Abnormal blood count reports have been examined in experimentally affected animals with high exposure to microplastics. Neutrophilia and polychromatic erythrocytes in animals indicating inflammatory response and anemia respectively and are caused due to microplastics toxicity generally observed in animals with chronic microplastic suffering. Microplastics provide platform to aquatic bacteria and serve as easy vehicle for transport in animal guts. Association between microplastics and microbes is complex as experimentally infected fishes have shown raised level of effective dose (ED_{50}) of tetracyclines than unaffected microplastic cultures predicting drug resistance relationship between microplastics and bacteria (Xiang et al. 2022). Some studies have declared microplastics as a vehicle in transfer of plasmid associated antibiotic resistance gene among bacterial colonies contributing its part in AMR (Arias-Andres et al. 2018; Sehnal et al. 2021). Microplastics commonly gain entry into the body through ingestion, inhalation and large wounds but they can't penetrate intact skin of animals and humans that usually allows particles of size <100nm to penetrate. An advanced form of microplastics has been discovered called nano particles that can even penetrate the skin, blood brain barrier and placenta causing brain and reproductive toxicities. Microplastics are not only major threat to aqua cultures and sea life but also present in atmosphere in dried form and play their role in air quality index as particulate matter (Xiang et al. 2022). Although there is negligible data on illness through microplastics and no mortality has been reported yet, it is the personal opinion of author that there will be an opportunity of extensive research in microplastics illnesses in future as fast as their production and utilization is growing and studies have been carried out in only 20% countries worldwide.

Climatic Changes and Resultant Microbic Mastitis

Climate change compromises quantity and quality of milk and udder health. Dairy animals face heat stress due to climatic change which is measured through Temperature Humidity Index (THI). Heat stress results in reduced feed intake, less milk production and promotes the growth of certain microbes resulting in sub-clinical mastitis and increased Somatic Cell Count (SCC) in milk allowing pathogens like *Arcanobacterium pyogenes, Truperella pyogenes* and *Mycoplasma* to inhabit udder and induce udder illness (Osei-Amponsah et al. 2020). Affected udder shedding high SCC in milk, can be identified in individual testing (2,50,000 cells/ml) or in herd testing which is considered economical. Increased temperature also affects the quality of milk (Sehnal et al. 2021). According to some studies conducted on Holstein, there was a decrease in different components of milk during summer months (Bernabucci et al. 2010; Baumgard and Rhoads Jr 2013). Decrease in the milk and milk protein by 0.06% to 0.12% and 0.1% to 0.5% was reported respectively. A sudden change in temperature either low or high, leading to cold stress or heat stress may result drop in milk production by 10% to 30% during first lactation and 5% to 20% during second or third lactation. Economic losses of dairy industry are evident from the climate changes.

Climate Change and Immunosuppression in Animals

Animals get affected by heat stress differently but the suppression of immune system is common which gives a greater room to infectious agent to cause infection and damage animal in multiple ways. Due to malnutrition in heat stress, cattle can go with poor differentiation of T and B lymphocytes and maldevelopment of lymphoid organs. Heat stress can affect embryogenesis disrupting the cells responsible for immune system of fetus and producing an immunocompromised individual. Heat stress at the end of gestation can result in less IgG level in the colostrum. Neonates receiving inadequate antibodies level via colostrum will be less immune. Heat stress can result in impaired antigen-specific humoral responses and significant decrease in B cells in bursa and splenic lymphocytes in poultry. This results in mineral deficiency like zinc, copper, iron and cobalt which causes conditions like anemia and leukopenia (Shukla et al. 2018). The changing water cycles have changed the trend of vector-borne diseases by altering life cycles, making it harder for animals to survive with compromised immune system. Even the sandstorms containing different oxides, dioxides and skin penetrating bacteria and fungi can affect animals badly (Middleton et al. 2019).

Effects of Food Security on Animal Health

The report of Intergovernmental Panel on Climate Change (IPCC) indicates that the extreme climate events such as drought, flood and storm have led millions of people to face malnutrition and food insecurity. Further, due to the devastating effects of these climate changes, the crop production is much lesser than the required quantity which leads to higher prices and lesser availability. The climatic change can prove devastating if left untreated and it will lead to dangerous consequences such as falling in the domestic food production leading to the increase in prices and undermining access of food. Crop production will decrease due to consequent reduced precipitation that will eventually lead to increase in food insecurity worldwide

Table 2: Impact of Climate Change on Meat Production from 1961 to 2018 where "t" denotes tons (Fróna et al. 2021)

Country	1961	2018	Absolute change	Relative change
Bangladesh	168900.0t	705745.00t	+536845.00t	+318%
Canada	1478414.00t	4893195.00t	+3414781.00t	+231%
Europe	30004080.00t	63845936.00t	+33841856.00t	+113%
Pakistan	365890.00t	3870230.00t	+3504340.00t	+958%
United states	16513033.00t	46832946.00t	+30319913.00t	+184%

(Butt et al. 2003). Climate has not only effects on agriculture but also has threatening impact on marine and fresh water ecosystem, water resources, wild life and forest products. People who rely on livestock, rivers, oceans and forests for living will eventually face the consequences due to severe climate variations (Devereux and Edwards 2004). According to IPCC variations in the climate will increase the average global temperature due to which the dry places will get more dry and wet places will get more humid. Animal feed consumes about 40% of the cropland of the global world. More than one third of the world's cereal production is consumed in animal feed. If there is shortage of cereal crops, it is quite obvious that it will eventually cost the animal health (Erb et al. 2012). The scale of economy linked with the non-internalization of health and climate costs allow cheap animal feed production based on single cropping without rotation of crops. Lower production can't fulfill the required consumption. The internal supply of feed is drastically reduced at farms due to pesticides and synthetic fertilizers that are used as a substitute. Pesticides are very harmful to animal health in terms of reproductive defects, liver and kidney damage and neurotoxicity. Lesser concentration of feed affects beef and dairy animals badly. During the winter season, a significant compartment of energy is used in the physiological maintenance as a result they have less energy left for milk production (Erb et al. 2012). Table 2 shows the impact of climate change on meat production from 1961 to 2018.

Global warming is the topmost factor that is causing decline in meat production. The climate impact on meat is greater than the past estimates. The climate crisis is the reason of the hunger. A recent study indicate that one-third of the global food production will be at risk by the end of the century if greenhouse gas emissions continue to rise (Masson-Delmotte et al. 2022). It has been estimated that there are 3 chickens for every human being in the planet. The production associated with livestock contributes 14.5% of the total greenhouse gases which originate in direct way from animals (39%) or indirectly by meat production. Climate change may affect the quality of meat in two ways; first is the direct effect on the metabolism of muscles and on organs during the exposure of heat and second is the management of poultry and livestock practices (Godde et al. 2021). Broilers of 14 days of age when grown, one at high temperature (33^0Cday and 27^0Cnight) and other at low temperature (23^0Cday time and 17^0C at night) concluded that the former birds had higher breast meat pH (Fletcher et al. 2000). Self-contradictory, a separate study indicated that the birds had lower pH when grown at high temperature and breast meat was pale and light red in color (Fletcher et al. 2000). The results were confirmed in Turkey Toms. High temperature breast meat was paler and had lower pH. Heat stress lowers the pH of thigh meat and raises the production of superoxide by mitochondria in the breast meat. Damage of muscles and skin tears are generally observed in broilers at high temperature (Fletcher et al. 2000).

Summary

Climate change is a natural phenomenon associated with human activities that disturbs natural ecosystems. Animals are adapting generation wise to the climatic fluctuations. Most highlighted form of climatic change is raised temperature curve and it is affecting animal health and welfare in multiple ways i.e., promoting drug resistance, acclimation of animals to alteration in metabolic changes, mastitis issues in dairy animals, enhanced number of immunocompromised organisms and compromised production in dairy as well as beef animals. It is the reason that THI is a considerable parameter today in dairy and poultry managements. Aquatic pollution especially through microplastics is modern form of climatic abuse that is affecting gut microbiota of animals. Genetically prepared breeds may prove fruitless sooner or later in future due to climate change. Sufferings of animal health is ultimately caused by crop production below the optimum capacity and insecure food chain. Climate change is directly affecting animal health and matter of disgust is that higher authorities are having fingers on their lips instead of releasing funds and promoting further research for welfare of animals.

REFERENCES

Ahmad I et al., 2021. Environmental antimicrobial resistance and its drivers: a potential threat to public health. Journal of Global Antimicrobial Resistance 27: 101-111.

Ali MZ et al., 2020. Impact of global climate change on livestock health: Bangladesh perspective. Open Veterinary Journal 10: 178–188-178–188.

Arias-Andres M et al., 2018. Microplastic pollution increases gene exchange in aquatic ecosystems. Environmental Pollution 237: 253-261.

Baumgard LH and Rhoads Jr RP, 2013. Effects of heat stress on postabsorptive metabolism and energetics. Annual Review of Animal Biosciences 1: 311-337.

Bernabucci U et al., 2010. Metabolic and hormonal acclimation to heat stress in domesticated ruminants. Animal 4: 1167-1183.

Butt T et al., 2003. Food security implication of climate change in developing countries: findings from a case study in Mali. Department of Agricultural Economics, Texas A & M University.

Camberlin P, 2017. Temperature trends and variability in the Greater Horn of Africa: interactions with precipitation. Climate Dynamics 48: 477-498.

Devereux S and Edwards J, 2004. Climate change and food security.

Erb KH et al., 2012. The impact of industrial grain fed livestock production on food security: an extended literature review. Commissioned by compassion in world farming. The Tubney Charitable Trust and World Society for the Protection of Animals, London, UK.

Fletcher D et al., 2000. The relationship of raw broiler breast meat color and pH to cooked meat color and pH. Poultry Science 79: 784-788.

Fróna D et al., 2021. Economic effects of climate change on global agricultural production. Nature Conservation 44: 117-139.

Godde CM et al., 2021. Impacts of climate change on the livestock food supply chain; a review of the evidence. Global Food Security 28: 100488.

Gonzalez-Rivas PA et al., 2020. Effects of heat stress on animal physiology, metabolism, and meat quality: A review. Meat Science 162: 108025.

Hayek MN, 2022. The infectious disease trap of animal agriculture. Science Advances. 8: eadd6681.

Huang Z et al., 2021. Microplastic: A potential threat to human and animal health by interfering with the intestinal barrier function and changing the intestinal microenvironment. Science of the Total Environment 785: 147365.

MacFadden DR et al., 2018. Antibiotic resistance increases with local temperature. Nature Climate Change 8: 510-514.

Masson-Delmotte V et al., 2022. Global Warming of 1.5° C: IPCC Special Report on Impacts of Global Warming of 1.5° C above Pre-industrial Levels in Context of Strengthening Response to Climate Change, Sustainable Development, and Efforts to Eradicate Poverty. Cambridge University Press, Cambridge, UK.

Middleton N et al., 2019. Sand and dust storms: underrated natural hazards. Disasters 43: 390-409.

Osei-Amponsah R et al., 2020. Heat stress impacts on lactating cows grazing Australian summer pastures on an automatic robotic dairy. Animals 10: 869.

Rahimi J et al., 2021. Heat stress will detrimentally impact future livestock production in East Africa. Nature Food 2: 88-96.

Sehnal L et al., 2021. Microbiome composition and function in aquatic vertebrates: small organisms making big impacts on aquatic animal health. Frontiers in Microbiology 358.

Shukla AK et al., 2018. Micronutrients in soils, plants, animals and humans. Indian Journal of Fertilisers 14: 30-54.

Tian M et al., 2021. Pollution by antibiotics and antimicrobial resistance in livestock and poultry manure in China, and countermeasures. Antibiotics 10: 539.

Vallianou N et al., 2019. Understanding the role of the gut microbiome and microbial metabolites in obesity and obesity-associated metabolic disorders: current evidence and perspectives. Current Obesity Reports 8: 317-332.

Wang J et al., 2021. The impact of microplastic-microbe interactions on animal health and biogeochemical cycles: A mini-review. Science of the Total Environment 773: 145697.

Xiang Y et al., 2022. Microplastics and environmental pollutants: Key interaction and toxicology in aquatic and soil environments. Journal of Hazardous Materials 422: 126843

3

Repercussions of Climate Change on Zoonoses and Food Security

AUTHORS DETAIL

Juan José Ojeda-Carrasco[1], Virginia Guadalupe García-Rubio[1], Laura Dolores Rueda-Quiroz[1], Pedro Abel Hernández-García[1], Enrique Espinosa-Ayala[1] and Ofelia Márquez-Molina[1]

[1]Centro Universitario UAEM Amecameca, Universidad Autónoma del Estado de México, México.
*Corresponding author: jjojedac@uaemex.mx

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INTRODUCTION

The increasingly changing conditions associated with climate change are significantly affecting the populations, in their physical integrity and basic subsistence conditions. The increase in environmental temperature, as well as other atmospheric variables such as precipitation, humidity, evaporation levels and wind, tend to favor the capacities of pathogens to spread and expand their geographic presence. In addition to this, the proliferation of vectors and the increase in contact between wild species, domestic animals and humans, together with environmental degradation and contamination of natural resources, are increasing the number of zoonoses and the risks that constantly threaten public health, animal health and the environment (Lindahl and Grace 2015; Siclari 2020).

The spread of diseases, the multiplication of reservoirs, the increase in zoonoses, the scarcity of drinking water and the impact on agricultural production are generating negative effects on food security throughout the world. The effect on the productive processes integrates a diversity of factors, including the loss of crops due to the flooding of soils, the increase in pests, prolonged droughts, the death of animals due to starvation or the development of diseases. Under these conditions, the increased demand for animal products faces a double challenge. On one hand, adaptations to the forms of livestock production to reduce their contributions to climate change, as well as increase productivity and guarantee food supply. Moreover, on the other, to face the adversities linked to climate change that are promoting the emergence and spread of pathogens, which in addition to affecting the health of animals, generate important consequences for human health and the availability and safety of food. To overcome these challenges, it is necessary to recognize that it is not only about producing more, but also producing in conditions that in addition to supply, guarantee the animal health, public health and food safety, seeking to care for the environment and to achieve its sustainability (Ojeda et al. 2022).

In this scenario, the *One Health* approach offers the possibility of facing the current complexities of the environments in which production takes place. This multisectoral and multidisciplinary approach applicable at all levels (global, regional, local) and proposes that to achieve optimal health results, it is necessary to recognize the interconnection that exists between animals, people and the environment. In recent years, this approach is gaining strength due to the identification of factors that have modified animal-human-environment interactions. Among other aspects, it highlights that the way in which human populations are in contact with wild and domestic animals is increasing, the opportunities for transmission of pathogens between animals, and from these to humans (zoonoses) is also increasing (Schneider et al. 2011; Guardo 2018).

Climate Change as an Undeniable Reference

One of the problems that have reached the greatest global consensus in recent history is Climate Change. An atmospheric condition in which the accumulation and increase in the concentrations of Greenhouse Gases (GHG) in the atmosphere are contributing to raising the temperature of the planet (global warming) and to the manifestation of extreme weather events that, seriously risk the future of life on the planet, if continue (IPCC 2001; Basso et al. 2021).

It is worrying that, for more than a decade, based on measurements of climate variability, experts in the field have concluded that if GHG emissions continue at the levels that were registered or continue to increase, they can lead to catastrophic effects. The 2001 report of the *Intergovernmental Panel on Climate Change* (IPCC) shows the degree of alteration of the planet based on three indicators including the concentration of GHG, the increase in environmental temperature and the rise in sea level. Between 1750 and 2011, GHG concentrations increased by 31% for carbon dioxide (CO_2), 151% for methane (CH_4) and 17% for nitrous oxide (N_2O). The increase in temperature has been gradual and sustained. Between 1983 and 1998, it increased between 4 and 8°C, with 1998 being the warmest year. Finally, the rise in sea level between 10 and 20 cm in a period of just under 100 years, mainly due to the reduction of non-

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polar glaciers and the thinning of Arctic ice (IPCC 2001). Since then, alterations to the planet associated with climate change are evident with more recurrent extreme weather events: stronger rainfall, more frequent, persistent and intense El Niño episodes, increased frequency and intensity of droughts, electrical storms, torrential storms and hail (Cepal et al. 2018).

To show the importance of climate change, the World Health Organization (WHO) has been insisting on highlighting the strong link that environmental conditions have on human health, within the framework of precautionary and equity principles (WHO 2018). For its part, the United Nations Environment Program (UNEP) refers to aspects of vulnerability, risks to the health of human groups and food security, in relation to the phenomenon of environmental change and the importance to reduce the risk of future pandemics (PNUMA 2020). According to recent scientific studies, climate change and climate variability affect human health, animal health, ecological systems, and socioeconomic sectors vital to sustainable development. Climate change represents an important additional factor of wear on ecosystems already affected by the growing demand for resources, unsustainable management practices and pollution, which in many cases can reach the same or greater magnitude than climate change (Fouque and Reeder 2019).

Under these weather conditions, environmental risks are increasing the vulnerability of populations and affecting their resilience. This underlines the need to analyze the threats of climate change from a multidimensional perspective, which includes the temporal dimension, synergies, geographic contexts, and all those variables that are determining factors, such as anthropogenic environmental deterioration. The close relationship between changes in climate is associated with environmental alterations caused by changes in land use, such as deforestation, replacement of forest areas, soil erosion, excessive logging and forest burning. These alterations are conducive to increasing the spread of diseases and risk factors for the health of both people and animals. Hence, the special emphasis on the importance of increasing the efficiency of the use of natural resources, the protection of biodiversity, the increase in agroecological resilience, as well as the improvement of the safety of food intended for human consumption. This requires to pay attention to the prevention, control and/or timely treatment of diseases in animals, especially considering that about 70% of infectious diseases that affect human health have an origin in animal sources (zoonoses) (Siclari 2020).

Impact of Climate Change on Zoonoses

Alterations in atmospheric and environmental conditions produced by climate change and the degradation of ecosystems are increasing the incidence of zoonoses. Climatic variability in temperature, humidity and rainfall levels, and its extreme manifestations, in addition to favoring the spread of pathogens and the increase in vectors, are harming fauna and flora species, increasing their susceptibility to developing diseases. Environmental degradation, generated by human activities, is altering life in natural habitats. There is increased competition for resources, migration of species and loss of biodiversity, which increases the exposure of resilient species to pathogens. The combination of these climatic and environmental conditions is determining the increase in diseases and many of these are zoonotic in nature. The invasion of natural habitats and contact with wild species that are natural reservoirs of many pathogens progressively increases the diseases that affect human health (Lindahl and Grace 2015).

Although pathogens have the ability to emerge by themselves but the increase in temperature due to global warming, gives greater impetus to this process. Under these conditions, viruses increase their mutation, being the ones that participate to a greater degree in emerging diseases. In addition to this, ecological factors of anthropogenic influence such as deforestation, excessive logging, depletion of aquifers and the alterations in land use have great influence on the increase in diseases. Among the emerging pathogens, protozoa and viruses have the highest proportions in the development of diseases, highlighting the fact that the probability of the emergence of zoonoses is almost twice that of non-zoonotic diseases (Taylor et al. 2001).

From the epidemiological point of view, the scope of the zoonoses will depend on the etiological agents, the reservoirs, modes of transmission and the susceptibility of the hosts. These scopes also depend on adverse environmental conditions that affect the resilience of the hosts, by increasing their vulnerability to contract diseases and promoting their spread. An important aspect is that climate change and the loss of biodiversity facilitate the jump of pathogens between one species and another, contributing to the spread of diseases in different animal and human populations. Depending on the prevailing conditions, the magnitude of appearance of zoonotic diseases can be variable. They can arise from regionally localized outbreaks (epizootics), the recurrent presence in geographic areas or population groups (endemics), the rapid and active spread of the disease in specific geographic areas (epidemics), or that the degree of affectation has global reach (pandemics) (Woolhouse et al. 2005).

The diversity, evolution and impact of many zoonoses position them as one of the main threats to the health of humans and animals. Of the recent events that affect public health, 70% are associated with zoonotic diseases. In addition to the fact that climate change favors the reproduction and expression of the inherent capacities of pathogens, environmental alterations are modifying the interrelationships between species in natural ecosystems (Schneider et al. 2011).

The increase in the reproduction and distribution of vectors and the decrease in species is amplifying the number of hosts towards other wild animals and from these to humans, due to increase in contacts. Population dynamics in ecosystems are changing due to biodiversity loss and resource scarcity.

Among others, rodents stand out as important reservoirs of various pathogens. In addition to its high reproductive capacity, the increase in populations is associated with the decrease in predators. In the face of adverse conditions, migration to other areas favors a greater spread of pathogens, especially in rural areas, increasing the risk of diseases in humans (Plowright et al. 2017; Carlson et al. 2022).

In this way, climatic variability, mainly related to the increase in temperature and changes in rainfall associated with climate change, are inducing changes in the life cycles, transmission mechanisms and colonization of new biological niches of pathogens and increasing the occurrence of diseases, changes in prevalence and increases in morbidity and mortality of animals and people. In the case of human beings, the greatest effects of zoonoses occur in the periphery of various climatic regions, coinciding with populations that are more receptive and with lower immune capacities, associated with conditions of marginalization and poverty, as well as the deficiency of health systems to establish adequate prevention and control measures (Fouque and Reeder 2019).

Climate Change and Animal Production

Climate change and changes in land use favor the spread of zoonoses, by generating the right conditions for viruses to transcend the barriers between wild and domestic species and increasing the potential risks for humans to develop diseases (Carlson et al. 2022). Of all the anthropogenic activities that contribute to climate variability and the factors that alter land use, animal production to meet the food demand of the human population plays a preponderant role (Cepal et al. 2018).

In 2006 in *Livestock´s Long Shadow*, the Food and Agriculture Organization of the United Nations warned about the multiplicity of impacts that the livestock sector produces on the environment. It assigns to animal production the responsibility of directly participating in climate change, pollution and environmental degradation (changes in land use, aquifer contamination, soil depletion, loss of plant cover) and the effects that this entails on the loss of biodiversity on the planet. Based on the analysis of information on the trends and factors associated with livestock production systems and the influence of livestock rearing on the Carbon and Nitrogen cycles, they offer options to encourage the development of measures aimed at mitigating the effects of the sector. Options include carbon sequestration to reduce carbon dioxide (CO_2) emissions through intensifying agriculture and reducing deforestation and the replenishment of organic carbon in soils, especially from degraded grasslands. Likewise, reduce methane emissions (CH_4) produced by enteric fermentation by using balanced and improved diets and efficient management of manure, which will also contribute in reducing nitric oxide (N_2O) levels. The set of proposed actions seek to reduce the emissions of these GHGs and reverse the environmental damage caused by livestock activity (Steinfeld et al. 2006).

Based on this, although it is true that climate change affects human and animal health, the ability to grow food and raise animals, livestock production contributes significantly to this climate change, due to the GHG emissions linked to different processes of this activity. Of the GHGs produced in nature (they do not include Hydrofluorocarbons, Perfluorocarbons and Sulfur Hexafluoride), the livestock sector has important contributions. CO_2 is produced by the aerobic decomposition of carbonaceous substances. CH_4 comes from enteric fermentation in ruminants, in which methanogenic microorganisms (bacteria and archaea) housed in the rumen participate, and from the decomposition of manure. N_2O emissions are associated with the use of nitrogenous fertilizers in crops destined for feed, the burning of biomass, and animal waste, which includes the urine of livestock. In addition to the volume of emissions, the importance of the agricultural sector is associated with the Global Warming Potential (GWP) of GHGs. The GWP is a factor that quantitatively represents the impacts generated at a global level, taking carbon dioxide as a reference unit, measuring the emissions of each in equivalents of this gas (CO_2-eq). The GWP of CO_2 is one, of CH_4 is 21, and of N_2O is 296 (Costantini et al. 2018; Cuatecontzi and Gasca 2019).

Steinfeld et al. (2006) estimated that, worldwide livestock activity was responsible for 9% of CO_2 emissions, due to changes in land use by transforming forest areas into pastures or areas for the cultivation of fodder. Likewise, about 37% of CH_4 from ruminant digestion, 65% of N_2O from manure, and 64% of ammonium emissions, which contribute to both acid rain and ecosystem acidification. In addition to its contribution to GHG emissions, the sector emphasizes other environmental problems related to the availability of water, eutrophication, the impact on the recharge of aquifers and the loss of biodiversity caused by deforestation, assigning a leading role of livestock production in global environmental problems.

Despite these circumstances, due to the great demand for foods of animal origin, livestock production represents a sector of large dimensions, dynamic, diversified and with an upward trend in productive and economic growth, in all regions. The main products include beef and milk from cattle and pork, meat and milk from small ruminants such as sheep and goats, buffalo meat and milk (mainly produced in the South Asian region) and chicken egg, although in some regions other types of birds are consumed. In regional world production, for 2020, the four regions that report the highest production are East Asia and Southeast Asia with 19.4 Million Tons (Mt), Latin America and the Caribbean region with 12.2 Mt, Western Europe with 10.4 Mt and North America with 10.1 Mt; while the one with the lowest production is Oceania, with only 1.6 Mt. As to be expected, this production contributes large GHG emissions, with differences between the regions linked to the degree of productive efficiency, the species that are produced and the capacities for managing waste and manure. As an example, it highlights the fact that East Asia and Southeast Asia produce 7.2 Mt of animal protein than Latin America and the

Caribbean region, the former contributes 1,576 million tons of CO_2 equivalent ($MtCO_2$-eq), corresponding to 20.94 % worldwide, while Latin America is the region with the highest contributions worldwide with 1,889 $MtCO_2$-eq (25.10%). In the case of Western Europe and North America, with very similar productions, emissions amount to 127 $MtCO_2$-eq (7.69%) and 604 $MtCO_2$-eq (8.03%), respectively (FAO 2020).

According to the World Livestock Environmental Assessment Model, emissions in kg of CO_2-eq per kg of protein vary depending on the type of livestock, which is decisive in the contributions of each region. In meat production, the one with the highest GHG emissions is buffalo meat, with 404 Kg of CO_2-eq/Kg, followed by bovine meat with 295 Kg of CO_2-eq/Kg, small ruminants with 201 Kg of CO_2-eq/Kg, pork with 55 Kg of CO_2-eq/Kg and chicken with 35 Kg of CO_2-eq/Kg. In milk production, the highest emission corresponds to buffalo milk (140 Kg of CO_2-eq/Kg), followed by small ruminants (148 Kg of CO_2-eq/Kg) and cattle (87 Kg of CO_2-eq/Kg) (FAO 2020).

Added to the GHG emissions generated by protein production are those from enteric fermentation and manure management, which vary depending on the species of livestock in question and the production systems, used. The large amounts of CH_4 produced by ruminants during feed digestion (methanogenesis), in 2020 reached 2.3 billion tons of CO_2-eq. In the case of manure from cattle, the most widely used for agricultural fertilization purposes, it is estimated that the total decomposition time is 4 years, generating an average of 8-9 Kg of N_2O per Ton/hectare applied, throughout these years (Basso et al. 2021). Inadequate manure management, in addition to aggravating climate change, also generates impacts on the environment and health by enhancing the conditions for the proliferation of pathogens, the accumulation of nutrients in the soil, by exceeding the capture capacity generating eutrophication, or causing its infiltration into surface or groundwater by runoff and leaching processes (Sánchez et al. 2020).

Livestock production generates high environmental impacts, which affect both its productivity and the stability of ecosystems, influencing the diversity of resources they have which include soil, water, air, energy and biodiversity. In the soil, it modifies the natural edaphic conditions (aeration, pH, fertility, organic matter content, moisture, structure, water table), by causing erosion, compaction and modifying the natural biological activity. In the case of water, the Water Footprint (WF) is very high, due to the high volumes that are required, affecting the water balance, as well as due to the contamination of natural sources and due to the use of rivers, lakes and lagoons as landfills. In the air, the emission of CO_2, CH_4 and N_2O contributes to global warming and climate change and pollution by suspended particles that alter the photosynthesis processes of plants, and therefore, the generation of energy. Finally, the severe modification of ecosystems to expand breeding spaces is causing serious damage to habitats and their biodiversity (García et al. 2022).

Directly related to climate change, the Carbon Footprint (CF), allows quantifying the environmental impact of livestock production, by providing an estimate of the total GHG emissions generated throughout the production chain. It encompasses from emissions associated with the metabolic and physiological processes of animals, to those variables related to production processes, such as the burning of fossil fuels used for the production, transformation and transportation of food, the consumption of electrical energy, refrigerants and synthetic fertilizers. To measure the level of the impact of livestock production, from the total HDC (integrating meat, milk and egg), the production of animal protein generated 7,520 Mt of CO_2-eq (FAO, 2020), which corresponds to 20.66% of total global emissions, compared to emissions associated with industrial products and processes that represent 9.10%, to set a benchmark (Basso et al. 2021).

Consequences of Climate Change in the Dimensions of Food Security

The effects of climate change are multivariate and diverse, since they not only affect the stability of ecosystems and their biodiversity, but also that of populations. The increasingly frequent and intense manifestation of extreme weather events is increasing risk factors. Natural disasters are increasing the vulnerability of populations due to the adverse effects they generate, both due to the loss of human lives and the impact on basic means of subsistence, due to the damage caused to crops, livestock and heritage assets. Added to these conditions are the risk factors associated with environmental deterioration. The modification of environmental conditions caused by human activities, together with climatic variability, favor the development and dispersion of pathogens, as well as the diversification of hosts. With this, the emergence and re-emergence of diseases that generate significant damage to human health, animal health and food safety, by undermining the availability of safe and quality food, as well as by the increase in zoonoses (Donoso et al. 2016; cepal et al. 2018).

The impact of climate change on livestock production includes the effects generated by variations in temperature, humidity and precipitation that subject animals to physiological stress processes. When there is enough food and water, the increase in environmental temperature causes the animals to reduce their consumption affecting the weight gain. In conditions of extreme drought, where food and available water are limited, animals experience progressive weight loss and dehydration that usually ends with the death of the animal due to starvation. In both cases, the physiological alterations tend to weaken the animals and make them more susceptible to developing diseases, becoming in many cases sources of infection from which the disease spreads, either by direct contact or through contaminated waste. Climate change also favors the spread of pathogens and vectors, which increases the development of diseases and affects the production chain and, therefore, food security (Sánchez et al. 2020).

In this way, climate change has effects on livestock production and food security, but also on the incidence and prevalence of diseases, many of which can reach significant degrees of affectation. In recent years various diseases, in addition to generating health problems negatively affected food security, due to the losses generated by the death or slaughter of sick animals in different regions of the world. Among these, African swine fever, a viral disease that caused the massive loss of pig populations, originally in Kenya and spread in many regions of the world and which recently had a re-emergence in the Dominican Republic (Carreón 2021). Bovine Spongiform Encephalopathy (BSE) or "mad cow syndrome", which between 1989 and 1992 caused the death of 200,000 adult dairy cows in the United Kingdom and spread to the United States, Brazil, Canada and most of European countries (SENASICA 2020). Scrapie in sheep that causes between 3-5% of deaths in flocks, present in Europe including the United Kingdom, Japan, Middle Eastern countries, Korea, Kenya, South Africa, and in the American Continent, in the United States, Canada and Colombia (CFSPH 2007). The outbreak of highly pathogenic avian influenza H7N3, which originated in 2012 in Los Altos de Jalisco, Mexico, which caused the slaughter of almost 22.5 million birds for both laying and meat production in this region. While many of these diseases are not transmissible to humans, BSE caused people who ate contaminated meat to develop a human variant known as Creutzfeld-Jakob Disease. Other diseases that originate as zoonoses or that are transmitted directly by animals, such as leptospirosis, echinococcosis, or brucellosis, have wreaked great havoc on human health due to the high rates of morbidity and mortality throughout the world (Ojeda et al. 2022). The most recent and significant case is the COVID-19 pandemic, whose most recent figures accumulate 607.6 million infected and 6.51 million deaths worldwide (WHO 2022a).

Diseases such as those referred can harm the health of animals and humans. When animal health is affected, there is a negative effect on food safety. According to the 1996 World Food Summit, “Food security exists when all people at all times have physical, social and economic access to sufficient, safe and nutritious food that meets their daily energy needs and food preferences to lead an active and healthy life” (FAO 2011). This condition integrates four dimensions: Availability, Access, Use, and Stability (FAO 2011).

Availability involves aspects of production, related to agroclimatic conditions of existence, determined by socioeconomic factors and net trade defined by the prevailing cultural aspects in each region. When it comes to production, climate change has direct effects. The rise in environmental temperature can generate physiological stress in animals, causing weight loss, dehydration, starvation and death, which reduces the protein available for human consumption. It also produces stress in plants, with high temperatures increases evapotranspiration (loss of water by evaporation and transpiration of the plant) and susceptibility to attack by pests. Prolonged droughts disable large areas for agriculture, while high concentrations of CO_2 will reduce the effectiveness of some herbicides. This will affect the production of fodder and the development of grasslands essential for feeding livestock. In the aspects of existence and trade, it can also influence the supply chains, transportation and distribution of food, both those used to feed animals and those produced for human consumption (FAO 2011; Cepal et al. 2018).

Access has to do with people having the means to purchase food to meet their needs. Climate change can affect families that are in a situation of poverty and marginalization, the source of income depends on the agricultural and/or livestock activities they carry out. Exposure to floods, droughts or other weather events, losses can be significant, reducing their income and purchasing power to a minimum to access a basic food basket. Due to this situation, climate change tends to exacerbate the vulnerability of these communities and their food security (FAO 2011; Cepal et al. 2018).

Regarding utilization, it refers to the body's use of the nutrients it receives with food. Although what is desirable is the development of good feeding practices through the consumption of nutritious foods, to ensure a good nutritional status, this will depend not only on eating habits or availability, but also on having access to them. However, when access to food is possible, extreme weather events such as excessive solar radiation and environmental temperature can produce pathophysiological changes that cause dehydration and loss of appetite, or food safety is not ideal, especially when there are no conditions to preserve them (refrigeration). A fundamental element of this dimension is the availability of drinking water. The effects of climate change can reduce its availability, but also influence its quality, by mixing drinking water sources with wastewater in a natural disaster (FAO 2011; Cepal et al. 2018).

Finally, stability seeks to guarantee the supply and continuous access to food. This dimension depends on the sustainability of the previous ones. Because of extreme climate change events, such as significant increases in temperature, droughts, floods, torrential rains and other natural disasters, food production is affected. The loss of crops and the death of animals due to heat stroke, lack of food, water and the spread of diseases, reduce the availability of food. When production is reduced, the relationship between supply and demand varies negatively, prices increase and therefore, for many communities, access to sufficient and safe food is reduced, which as a whole affect’s stability, by not be able to guarantee its supply, availability and access (Cepal et al. 2018).

As can be seen, climate change directly or indirectly affects each of the dimensions of food security. One aspect that has been gaining special relevance is that referring to food safety and its relationship with human health. Some illnesses result from secondary contamination of food during transportation, storage, processing for sale, or during preparation. However, the development of zoonoses is associated with the consumption of meat and other products from animals that carry pathogens. The increased consumption of exotic species raw or semi-raw meat, the consumption of animals whose causes of death are unknown (very frequent in rural areas that are dedicated to small-scale production), can be a source of emerging or re-emerging diseases, such as COVID-19, which is postulated to have originated from the consumption of bats. This has given special importance to Foodborne Diseases, whose incidence and prevalence is increasing (Taylor et al. 2001; Schneider et al. 2011; Siclari 2020).

According to the WHO, climate change generates important effects on the host-agent-environment interface. The pathogens present in wild species as their natural reservoirs are spreading to other species due to the loss of biodiversity and environmental alterations. The increase in vectors, atmospheric warming and meteorological events are also contributing to the spread of diseases that affect plants, animals and humans. Attention has focused on viruses, as these are the pathogens associated with a greater number of zoonoses. The three main routes of food contamination by viruses are animal feces and sewage from humans, people handling infected food, and animals. Factors that contribute to the increase in zoonoses include the appearance of pathogen variants, imbalances in ecosystems, changes in agricultural practices and production systems, as well as in food processing and distribution. Social factors also play an important role in the increase in zoonoses, due to the invasion of natural habitats, the globalization of food production and distribution, the increase in the movement of people from one place to another, changes in habits food, by integrating the consumption of meat from wild animals and demographic factors. (WHO 2008).

All these factors are promoting the zoonotic spill, that is the increase in the transmission of pathogens from vertebrate animals to humans (Plowright et al. 2017), as a result of climate change that is favoring the expression of the capacities of pathogens, that have been transported through food, increasing the risk of developing zoonoses through this route, with serious consequences for health. For this reason, the repercussions of climate change are very broad, affecting livestock production systems, production and supply chains, food security and human health, due to the increase in the incidence and prevalence of Foodborne Diseases (Donoso et al. 2016).

The Role of “One Health” in Food Security

Having enough quality and quantity of food is essential for a healthy life. Addressing food security that guarantees the availability, access, health and stability of food is essential for human health. Carrying out sustainable production processes represents the opportunity to achieve competitive and productive improvements, through the efficient use of resources. This would make it possible to simultaneously generate a lower environmental impact, ensure animal welfare and guarantee food security for the benefit of producers and their communities, through adequate management that promotes environmental, human and animal health (WHO 2022b).

The One Health approach offers these possibilities by promoting a transdisciplinary and multisectoral approach to the control of zoonoses, the restoration of balance in ecosystems and human and animal health. One of the main concerns of One Health is food safety estimating that every year around the world, one in ten people gets sick from the consumption of contaminated food, while 430,000 people die from this cause. The main interest is the relationship established between animal health and food safety, since the routes of exposure to foodborne diseases are associated with contact with sick wild or domestic animals or through the consumption of food and products from these (WHO 2022b). This is especially important if considered that in addition to climatic and environmental changes that favor the potential of pathogens, the vertiginous increase in world trade and the mobility of people, coupled with population growth, are promoting the massive production of food, as well as marketing chains throughout the world. These situations increase health risks, due to the use of antibiotics, food additives, pesticides and other contaminants used to speed up processes and increase production volumes (Schneider et al. 2011).

International efforts to establish regulatory measures for the ordering of production processes and the marketing of food products have not reached the same level of progress and consolidation in all countries. The purpose is to implement control standards that guarantee food safety and pathogen free (innocuous). However, the heterogeneity of criteria and the differences in installed capacities, both technical and operational, keep the risks latent contributing to the emergence and spread of diseases on a global scale (Guardo 2018).

Conclusion

The environmental alterations produced by climate change and the degradation of ecosystems favor the multiplication of reservoirs, the spread of diseases and the increase of zoonoses. The repercussions on production are generating negative effects on food security throughout the world, increasing the vulnerability of populations. The challenges they face include adapting forms of production to reduce contributions to climate change, increase productivity, promote the efficient use of resources, protect biodiversity and increase agroecological resilience. It is not just about producing more, but doing so in conditions that, in addition to supply, guarantee animal health, public health and food safety, seeking to care for the environment and to achieve its sustainability.

REFERENCES

Basso LA et al., 2021. Estado de los gases de efecto invernadero en la atmósfera según las observaciones mundiales realizadas en 2020. Boletín de la Organización Meteorológica Mundial de la ONU.

Carlson CJ et al., 2022. Climate change increases cross-species viral transmission risk. Nature 607: 555–562.

Carreón NR, 2021. Reaparece la peste porcina africana. Boletín UNAM-DGDC, 10 de agosto de 2021. https://www.dgcs.unam.mx/boletin/bdboletin/2021_644.html

Cepal et al., 2018. Cambio climático y seguridad alimentaria y nutricional en Centroamérica y la República Dominicana: Propuestas metodológicas, Comisión Económica para América Latina y el Caribe; pp: 156.

CFSPH, 2007. *Scrapie*. The Center for Food Security and Public Health.

Costantini A et al., 2018. Emisiones de gases de efecto invernadero en la producción ganadera. Ciencia e Investigación 5: 47-54.

Cuatecontzi DH and J Gasca, 2019. Los gases regulados por la Convención Marco de las Naciones Unidas sobre el Cambio Climático. Instituto Nacional de Ecología y Cambio Climático, México.

Donoso S et al., 2016. Zoonoses transmitted by food can affect its epidemiology, as a result of climate change and process of globalization. Chilean Journal of Agricultural and Animal Science 32(2): 149-156.

FAO, 2011. Food Security: Information for decision-making. Food and Agriculture Organization of the United Nations; pp: 4.

FAO, 2020. Global Livestock Enviromental Assesment Model (GLEAM). Food and Agriculture Organization of the United Nations; pp: 121.

Fouque F and Reeder JC, 2019. Impact of past and on-going changes on climate and weather on vector-borne diseases transmission: a look at the evidence. Infectious Diseases of Poverty 8(1): 51.

García RVG et al., 2022. Impacto del sector pecuario en la generación de gases de efecto invernadero: Desafíos para una ganadería sustentable [en] García RVG (Comp.) Potencialidades de la ovinocultura y los hongos comestibles (*Pleurotus* spp.) en la seguridad alimentaria y el desarrollo rural. Laberinto Ediciones, México; pp: 203-243.

Guardo M, 2018. The One Health approach more essential than ever before. Revista Peruana de Medicina Experimental y Salud Pública 35: 4.

IPCC, 2001. Third Assessment Report-climate Change, 2001. The Scientific Basis: Summary for Policymakers. A Report of Working Group I of the Intergovernmental Panel on Climate Change”. UNEP-WMO, 7.

Lindahl JF and Grace D, 2015. The consequences of human actions on risks for infectious diseases: a review. Infection Ecology and Epidemiology 5(1): 10.3402.

Ojeda CJJ et al., 2022. Principales enfermedades que afectan la productividad ovina e inocuidad alimentaria [en] García RVG (Comp.) Potencialidades de la ovinocultura y los hongos comestibles (*Pleurotus* spp.) en la seguridad alimentaria y el desarrollo rural. Laberinto Ediciones, México; pp: 339-419.

Plowright RK et al., 2017. Pathways to zoonotic spillover. Nature Review Microbiology 15: 502–510.

PNUMA, 2020. El PNUMA intensifica su trabajo para reducir los riesgos de pandemias a través de la protección ambiental. Programa de las Naciones Unidas para el Medio Ambiente-ONU.

Sánchez MB et al., 2020. Causes and consequences of climate change in livestock production an animal health. A Review. Revista Mexicana de Ciencias Pecuarias 2: 126-145.

Schneider MC et al., 2011. Importance of animal/human health interface in potential Public Health Emergencies of International Concern in the Americas. Revista Panamericana de Salud Pública 29(5): 371-379.

SENASICA, 2020. Encefalopatía espongiforme bovina. Servicio Nacional de Sanidad, Inocuidad y Calidad Agroalimentaria, Gobierno de México.

Siclari BPG, 2020. Amenazas de cambio climático, métricas de mitigación y adaptación en ciudades de América Latina y el Caribe, Comisión Económica para América Latina y el Caribe (Cepal); pp: 86.

Steinfeld H et al., 2006. Livestock’s long shadow. Environmental issues and options, Food and Agriculture Organization of the United Nations (FAO); pp: 390.

Taylor LH et al., 2001. Risk factors for human disease emergence. Philosophical Transactions of the Royal Society 356(1411): 983–989.

WHO, 2008. Viruses in food: Scientific advice to support risk management activities. Meeting Report: Microbiological Risk Assessment, series 13.

WHO, 2018. Health, environment and climate change. World Health Organization, Report of the Director-General, 144th Session of the Executive Board, 5 Dec 2018.

WHO, 2022a. Coronavirus disease (COVID-19) outbreak, World Health Organization, Press Conference, 7 Sept 2022.

WHO, 2022b. A health perspective on the role of the environment in One Health, World Health Organization, Regional Office for Europe, White Paper 29 Jun 2022

Woolhouse MEJ et al., 2005. Emerging pathogens: the epidemiology and evolution of species jumps. Trends in Ecology and Evolution 20(5): 238–244

Climate Change and the Resulting Waterborne Diseases

AUTHORS DETAIL

Arooba Mubeen, Syeda Ayesha Batool Bukhari,
Ayesha Fakhri and Maryam Aziz

University of Veterinary and Animal Sciences, Lahore;
Department of Environmental
*Corresponding author: aroobamubeen955@gmail.com

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INTRODUCTION

It is progressively acknowledged that climate change not only serves as a threat to the environment but also has adverse implications on public health and well-being. This change disrupts the natural balance of ecosystems and is subjected to varied consequences on human health determinants (Levy et al. 2018).

Climate change is characterized by changes in temperature, frequency, and intensity of precipitation, snowmelt, and snow cover and subsequent alterations in droughts, floods, and sea levels. This affects waterborne illnesses as high temperatures change the virulence, replication, and survival of the pathogens, extreme precipitation can agitate pathogens, and the capacity of water and sanitation infrastructure gets affected. Moreover, enhanced droughts increase pathogen concentration in water bodies (El-Sayed and Kamel 2020). The Intergovernmental Panel on Climate Change (IPCC) states that there is "very high confidence" that increased risks of food- and waterborne diseases can be expected "if climate change continues as projected across the representative concentration pathway (RCP) scenarios until mid-century" (Levy et al. 2018).

Major waterborne diseases triggered by climate change include but are not limited to Cholera and diarrhoeal diseases such as Salmonellosis, Giardiasis, and Cryptosporidiosis and also spread by E. coli. According to the global burden of disease study in 2015, it was projected that unsafe water consumption brings about 1.2 million deaths and 1.1 million deaths due to diarrhoeal diseases. Waterborne illnesses, specifically diarrhoeal diseases serve as the second major death cause among children below age 5; furthermore, these diseases are the second leading cause of death and ailments in countries with low-income rates. Globally climate change is potentially a threat to the downward spiral of waterborne diseases (Levy et al. 2018). Climate change may induce health impacts through different pathways and processes that include:

I. Direct pathways, i.e., extreme precipitation and sea level rise, leading to the increase in fecal-oral pathogens and droughts that affect the concentration of the pathogenic organisms.
II. Indirect pathways, i.e., increased temperature and humidity, affect pathogens' survival, replication, and generation time (Cissé 2019).

The impact of climate change on waterborne diseases is not only due to the disruption in environmental parameters but also to underlying socioeconomic factors, including poor infrastructure and lack of sanitation and hygiene facilities (Levy et al. 2018). Developing countries are more prone to the devastation of these deteriorating impacts of climate change, as there are no adequate facilities and a lack of data on how climate change affects their systems. Furthermore, developed nations should consider themselves responsible for this harm due to the overconsumption of energy to generate revenue (Hunter 2003).

This study reviews and summarizes the literature on the possible impacts of climate change on waterborne diseases. The emphasis of this chapter is on how climate change is contributing to disease spread and transmission of waterborne diseases.

Climate Change and Resulting Extreme Weather Events

Generally, the weather is not a hazard, but in some cases, it can be deadly and disturbing. These kinds of weather are usually termed extreme weather, which results in direct, abrupt, and undesirable effects on people, property, and structures. Commonly the events of hurricanes, tornadoes, long-term hot and cold conditions, extreme precipitation, hailstorms and natural disasters like floods and droughts are categorized as extreme events. Climate change refers to the long-term experiential alterations in temperature and weather patterns. According to Intergovernmental Panel on Climate change (IPCC), 20-40% of the world's population is living in regions where the target value of 1.5°C in relevance to the pre-industrial era is crossed by the decade 2006-2015, at least one season which means that the world is undoubtedly experiencing the impacts of climate change. The temperature rise resulted in changes in humans and natural systems, including increased droughts, floods, precipitation in some areas, sea-level rise due to snowmelt, and a decrease in snow cover (McBean 2004).

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Climate change and global warming are used interchangeably, but both terms have different meanings. Global warming is just another phenomenon associated with climate change. Global warming refers to the increase in the temperature of the planet Earth since the industrial revolution (El-Sayed and Kamel 2020). This increase in temperature has many dire consequences on natural systems, leading to an increase in certain natural disasters directly linked with climate change. Extreme precipitation events have become more common worldwide due to an increase in average temperature resulting from global warming. 2010 is considered the warmest year worldwide and the wettest year since 1900. Due to the prevalence of extreme temperatures, 19 countries set new high-temperature records. The result of these high temperatures was the increase in extreme weather events, which included heat waves in Russia that resulted in wildfires and killed 56,000 people. In China, these extreme temperatures lead to the century's worst drought in Yunnan province. In the USA, the 2010 summer months featured record-breaking heat. In 2010, many areas received heavy rainfall and flooding. Most affected areas due to this weather pattern shift include Pakistan, where flooding in the Indus valley displaced millions of people and created havoc in society. Rio de Janeiro is also included among those countries affected by this change and received the heaviest rainfall in 30 years, leading to hundreds of deaths. The effects of climate change continued to affect people globally as in 2011; the US experienced historic floods; Texas experienced the driest 12 months of history, and record-breaking tornado events (Huber and Gulledge 2011).

Climate change is likely to increase water stress and can hamper the quality of water in some areas, which can lead to increased cases of waterborne illnesses. Studies have shown a correlation between the increase in average annual temperatures with the increase in the incidence of diarrhoeal diseases (Hitz and Smith 2004). In Arctic regions, there is a direct linkage between the increase in temperature and the risk of gastric diseases as the permafrost thawing speeds up the intrusion of sewage water into drinking and recreational water bodies (Smith et al. 2015).

Adaptation to climate change and mitigation of greenhouse gases is required to limit global warming and to cope with the risk of extreme weather (Huber and Gulledge 2011). In addition, there is a need to reduce vulnerability and strengthen the adaptive capacity of vulnerable communities by developing strong coordination between the stakeholders of international treaties and agreements (Mirza 2003).To limit climate variability, the Conference of Parties at Glasgow made conclusive consideration to restrict the planet's warming to 1.5°C. This is done by immediate, profound, and sustained reductions in worldwide greenhouse gas emissions, precisely a 45% reduction in carbon dioxide concentration by 2030 as compared to the level of carbon dioxide in 2010 and net zero around the mid-century along with this decline in other potent greenhouse gases are mandatory (Lennan and Morgera 2022).

Climate Change and its Impact on the Waterborne Disease Pathway

Most of the research in this relevance has focused on the impacts of altered weather parameters on the survival and proliferation of waterborne pathogens. The literature reviewed during this research agrees that variations in temperature and rainfall are the key factors responsible for increasing incidence rates of waterborne illnesses. Enhanced droughts and floods, which are consequences of low and heavy rainfall, respectively, have immense health impacts. High temperatures increase the growth of pathogens in water. Multiple waterborne diseases are likely to have a high incidence rate at elevated ambient temperatures. In Zanzibar 1-degree increase in temperature resulted in an increase in the cases of cholera by two-fold (Reyburn et al. 2011). Correspondingly, a systematic review studying the associations among climatic drivers of Diarrheagenic E coli concluded that the incidence of the disease under study increased with the increasing ambient temperature (Philipsborn and Ahmed 2016). Escherichia coli O157:H7 in Canada because of heavy rainfall and subsequent floods affected 1000 people; some died, and others were admitted to hospitals and recovered. A study conducted by an American concluded that 51% of the diseases occur due to heavy rainfall because the rainwater flows through different channels that are not usually used by the water, where cattle graze and fecal residues move with water; furthermore, it may leak into water bodies and contaminate them (Hunter 2003). The association of the El Nino period of 1990 with cholera incidence provides evidence of the relationship between the increase in temperature and the resultant increase in the incidence of waterborne infections (Nichols et al. 2018). To sum up, most pathogens, specifically bacteria, proliferate speedily in warm environments. Hence, increasing global mean Earth temperature and long summers in various parts of Earth due to climate change are aiding in high rates of waterborne illnesses.

Rainfall also plays an influential role in waterborne disease outbreaks. Heavy rainfall stimulates the mobilization of pathogens and hence makes them widespread. A recent study of precipitation and waterborne illness in the United States found that more than half the waterborne disease outbreaks in the United States during the last half-century followed a period of extreme rainfall (Charron et al. 2004). Similarly, in Bangladesh, it was studied that a 10mm high rainfall above the threshold resulted in a 14% rise in cholera cases. It happens because of the large amount of run-off produced and the high risk of contamination it poses to water reservoirs (Hashizume et al. 2008). Less rainfall concentrates the pathogens in limited water areas. Sanitation and water treatments become less effective in this case. Resultantly, the environment-to-person transmission of pathogens becomes more likely to occur. However, the reviewed literature lacked quantifiable evidence to support the argument that climate change is increasing the risk of waterborne illnesses.

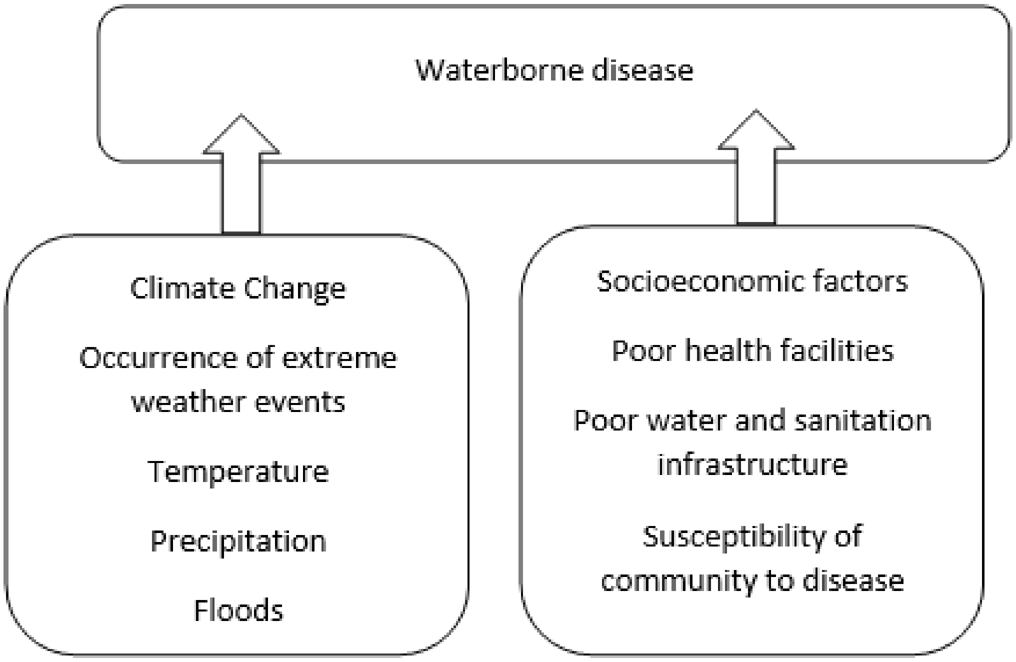
Waterborne disease
Climate Change
Occurrence of extreme weather events
Temperature
Precipitation
Floods
Socioeconomic factors
Poor health facilities
Poor water and sanitation infrastructure
Susceptibility of community to disease

Fig. 1: Factors contributing to the increase in cases of waterborne diseases

However, the suggestive evidence showing shifted precipitation patterns and temperature conditions; agrees that this climate change is negatively affecting the downward spiral of these infections achieved by human efforts. Hence, this climate change is projected to have adverse health impacts.

Cholera rises when the plankton thrives more with rising temperature, as in the case of El-Nino when sea surface temperature rose, and Cholera cases got a peak in Asia and South America (Hunter, 2003). Vibrio organisms responsible for the cause of Cholera thrive in warm water, and it was found that the Baltic Sea is favourable for the incidence of Cholera. It is evident that increased temperature and melting of glaciers change the habitats of organisms, so in response, the patterns of disease also alter. Nevertheless, the spread of Cholera can be prevented by improving the sanitation system (Leddin and Macrae 2020).

There is enormous evidence that excessive precipitation is associated with gastrointestinal illness; furthermore, the proliferation of cryptosporidiosis is linked with enteric diseases (Lipp et al. 2002).

Vector-borne illnesses are affected by alterations in climatic factors like temperature, humidity, precipitation, and wind, and Malaria is one of them. Therefore, the disruptions in these climatic variables aggravate the transmission of Malaria (Li and Managi 2022). The implications of climate change on the spread of dengue are also worsening. Rising temperature affects the dengue virus's generation and hatching duration as both become more rapid with increased temperature due to global warming. It is predicted by climate change scenarios that the average temperature will rise from 33°C in India and African Sahelian regions by 2050. However, this analysis was qualitative and does not speculate on vector competence, which is very susceptible to extreme high and low temperatures. So, we need more data to incorporate into climate models to enhance our ability to predict the effects of climate variability with more certainty (Rocklöv and Tozan 2019). The relationship between the spread of Malaria and temperature does not support a linear trend because malarial transmission aggravates by specific temperatures and then collapse when temperatures rise even high. Hence, both rise and fall in temperature are not appropriate for the survival of the vector responsible for malaria transmission (Li and Managi 2022).

Socioeconomic Factors Affecting the Spread of Waterborne Diseases

Along with the impacts of climate change, certain socioeconomic factors also contribute to the increase in the incidence of waterborne illnesses. An important factor in this case is the increase in the number of people who are more vulnerable to waterborne pathogens due to the prevalence of other diseases such as HIV and cancer patients whose immune systems have become weak. Another cause is the deterioration of public health facilities and the inappropriate application of initiatives in water, sanitation, and hygiene (Theron and Cloete 2002). The changes in waterborne disease epidemiology due to climate change will be more pronounced in locations where the disease burden is already high and where there are inadequate waste treatment facilities, water and sanitation infrastructure, and health systems (Levy et al. 2018). As per mentioned in Fig. 1.

Conclusion

Sufficient evidence has been collected to suggest that climate changes, especially heavy rainfall and progressively increasing high temperatures due to global warming, can potentially increase morbidity and mortality of food and waterborne diseases. Based on the accumulated evidence to date, it is concluded that not only the variations in climatic parameters, i.e., precipitation, temperature, humidity, and drought but the poor sanitary conditions in developing countries also increase the risk of food and water borne diseases. Therefore, extensive research is needed to improve sanitary facilities and systems in low-income countries to cope with the drastic climate changes. Research efforts can now identify how and where to implement the interventions of both social and economic value to reduce the risk of food and waterborne diseases.

REFERENCES

Charron DF et al., 2004. Vulnerability of waterborne diseases to climate change in Canada: A review. Journal of Toxicology and Environmental Health - Part A 67(20–22): 1667–1677.

Cissé G, 2019. Food-borne and water-borne diseases under climate change in low- and middle-income countries: Further efforts needed for reducing environmental health exposure risks. Acta Tropica 194: 181–188.

El-Sayed A and Kamel M, 2020. Climatic changes and their role in emergence and re-emergence of diseases. Environmental Science and Pollution Research 27(18): 22336–22352.

Hashizume M et al., 2008. The effect of rainfall on the incidence of cholera in Bangladesh. Epidemiology 19(1): 103–110.

Hitz S and Smith J, 2004. Estimating global impacts from climate change. Global Environmental Change 14(3): 201–218.

Huber DG and Gulledge J, 2011. Extreme Weather and Climate Change Understanding the Link, Managing the Risk. Science and Impacts Program. Center for Climate and Energy Solutions 2011: 1–13.

Hunter PR, 2003. Climate change and waterborne and vector-borne disease. Journal of Applied Microbiology Symposium Supplement 94(32): 37–46.

Leddin D and Macrae F, 2020. Climate Change: Implications for Gastrointestinal Health and Disease. Journal of Clinical Gastroenterology 54(5): 393–397.

Lennan M and Morgera E, 2022. The Glasgow Climate Conference (COP26). International Journal of Marine and Coastal Law 37(1): 137–151.

Levy K et al., 2018. Climate Change Impacts on Waterborne Diseases: Moving Toward Designing Interventions. Current Environmental Health Reports 5(2): 272–282.

Li C and Managi S, 2022. Global malaria infection risk from climate change. Environmental Research 214(3): 114028.

Lipp EK et al., 2002. Effects of global climate on infectious disease: The cholera model. Clinical Microbiology Reviews 15(4): 757–770.

McBean G, 2004. Climate change and extreme weather: A basis for action. Natural Hazards 31(1): 177–190.

Mirza MMQ, 2003. Climate change and extreme weather events: Can developing countries adapt? Climate Policy 3(3): 233–248.

Reyburn R et al., 2011. Climate variability and the outbreaks of cholera in Zanzibar, East Africa: A time series analysis. American Journal of Tropical Medicine and Hygiene 84(6): 862–869.

Rocklöv J and Tozan Y, 2019. Climate change and the rising infectiousness of dengue. Emerging Topics in Life Sciences 3(2): 133–142.

Smith KR et al., 2015. Human health: Impacts, adaptation, and co-benefits. In: Field CB, editor. Climate Change 2014 Impacts, Adaptation and Vulnerability: Part A: Global and Sectoral Aspects; pp: 709–754.

Theron J and Cloete TE, 2002. Emerging waterborne infections: Contributing factors, agents, and detection tools. Critical Reviews in Microbiology 28(1): 1–26.

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Sustainable Control of Contaminated Water

AUTHORS DETAIL

Hafiza Saba Javed[1]* and M. Adnan Sabir Mughal[2]

[1]Ibn-e-Sina group of College, Jaddah, Saudi Arabia
[2]University of Agriculture, Faisalabad, Pakistan
*Corresponding author: alizaahemad789@gmail.com

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INTRODUCTION

Water is the basic unit of life. The composition of water is based on two molecules: oxygen and hydrogen, but the addition of other substances in the water leads to its damaging effects, called pollutants or contaminants.(De Jong et al. 2009) These contaminants manage water quality and sustainability. Major categories of water include:

i) Surface water (lakes, streams, rivers, reservoirs, wetlands)
ii) Ground Water (indwelling from the ground)
iii) Wastewater (industrial, household)
iv) Storm Water (Rain, snowmelt)
v) Oceans

In multiple situations, water may not take into account the contaminated, but it depends on the degree of impurity, its volume, and its buffering ability. (Clement and Julius 2012) A certain number of contaminants are essential for marine and aquatic life and also for humans including calcium, iron, and magnesium. Pure and distilled water do not have these contaminants (Robertson et al. 1991) Various chemical contaminants to be analyzed for the standard quality of water have been described in Table 1.

Water Quality Standards

There are two fundamental types of water quality management in the control of water contaminants i.e., one type deals with the quality of received water supply which is believed as stream standard and another type deals with wastewater discharged from any source. This discharge of wastewater into rivers, streams, and freshwater is called "effluent standards." The latter is becoming more prevalent as a benchmark for industrial effluents (Kelly 1976).

Stream Standard Dilution

Stream standard dilution is the dilution for the given unit volume of waste discharge. This method is outmoded in different developed countries because a similar amount of waste volume holds diverse types of pollutants with different amounts. This method may be effective, if the same amount or equal volumes of receiving water treated (Blanchoud et al. 2007).

Effluent Standard

The more prevalent stream standard procedure uses limited values of specific substances when mixing with the stream water. It was a quite widespread practice in the past to set the quality criteria for beneficial use of the stream, such as drinking, swimming, fishing, irrigation, and household use. Water quality standards are generally set and approved by Federal Government Agencies but there is considering variation from country to country according to needs and standards. Water quality must be related to the quantity of flow in the stream and the assimilation of pollutants without contravening water quality standards. For example, how many cities present across the rivers, and what variability of pollutants assimilation in these cities? (Kilvington et al. 2004).

Different Aspects of Water Contamination from Different Sources

Biological Aspects of Water Pollution

The biological consequences of the pollution are often longer and more persistent after the evidence of physical and chemical contaminants disappears. The quality evaluation must include a biological analysis. There are multiple biological parameters involved.

1. Bacterial Growth

Bacterial growth has seven distinct phases, but the sigmoid growth curve is significantly useful on the relative pollution scale. Bacterial growth, multiplication, and death occur under ideal conditions, based on availability of food and suitable temperature (Boulding and Ginn 2016). The oxidation of organic matter occurred due to presence of bacteria in the streams, and freshwater reservoirs. The ideal situation is when no toxic elements are present and bacterial

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Table 1: Chemical components in diverse types of water (Clement and Julius 2012)

Chemical components	Rainwater	Surface soft	Surface hard	Ground hard	Ground soft
pH	6.8	6.9	7.8	7.4	6.6
Calcium	16 mg/l	30 mg/l	80 mg/l	142 mg/l	29 mg/l
Magnesium	3 mg/l	16 mg/l	40 mg/l	59 mg/l	32 mg/l
Sodium/ potassium	6 mg/l	9 mg/l	19 mg/l	20 mg/l	26 mg/l
Bicarbonates	12 mg/l	42 mg/l	106 mg/l	143 mg/l	60 mg/l
Sulfate	10 mg/l	12 mg/l	38 mg/l	59 mg/l	17 mg/l
Chlorides	5 mg/l	7 mg/l	23 mg/l	23 mg/l	23 mg/l
nitrates	0.1 mg/l	1.5 mg/l	0.4 mg/l	0.06 mg/l	Nil

death is under the logarithmic phase. They die according to the number of multiplications. There are distinct factors directly associated with bacterial growth including sedimentation of aggregates, sewage water supply, availability of optimum temperature and turbid water which increases the bacterial growth while flowing water, presence of protozoa and sunlight decreases the bacterial growth. All these favorable conditions directly affect the bacterial growth in water (Brick et al. 2004).

2. Viral Contaminants

Bacterial elimination is possible with different methods of growth retardation, but viruses are more persistent in fresh water. Commonly identified groups are rotavirus, polio, adenovirus, hepatitis A, calicivirus, astrovirus, reovirus, coronavirus, enterovirus, and coxsackievirus. Sewage water is estimated to contain seven thousand viruses per liter depending on the season’s warmth and wastewater dilution. Different viral groups are the causative agents of gastroenteritis, hepatitis, poliomyelitis, and other infections in humans. There are more than one hundred viruses excreted through human feces, and the contamination of drinking water with sewage causes multiple viral diseases. Viral inactivation treatment reduces the viral contamination from water. Chloramines are used to treat viral contamination in the water (Brick et al. 2004).

3. Algae and Protozoa

The normal freshwater lakes, streams, rivers, and other resources have an enumeration of algae, blue algae, protozoa, and other microorganisms. But the higher concentration of algae in freshwater reduces the ultraviolet rays of sunlight which increases the growth of other microbes. In the flowing water, there are fewer chances of algae growth but higher chances of protozoan species (Theodore 1990**).** The common diseases caused by a range of pathogens have been enlisted in the Table 2.

Hydrological Consideration

The physical characteristics of channels contributed to the control of deoxygenation, bacterial death rate, benthal decomposition, and reaeration. These physical characteristics in small freshwater resources can be figure out directly. The determination need not to be precise but dependent on the discharge of pollutants and time passage. Physical bodies sources include municipal waste, industrial waste lodge, drains of discharges, agricultural drainage, household activities, and organic nutrients. The immediate oxygen demand reduces, effecting directly on BOD which significantly increases within five days. The analysis of BOD (biochemical oxygen demand) and COD (chemical oxygen Demand) in water sample determines the quality of water. Sludge deposits and accumulation produces high demand of O_2 while the growth of bed extract causes the accumulation of organic matter, which produces a very sharp drop in dissolved $O_{2.}$ The abnormality of biological adsorption and oxygen demand may not be detected directly in the freshwater. Algae during the daylight hours give off oxygen as a by-product of photosynthesis, which may use at the night, but oxygen is low at night as photosynthesis stops (Seiler et al. 1999).

Contributing Factors to Self-purification of Water (Seiler et al. 1999)

1. Temperature is the major contributing factor as high temperatures reduces the amount of dissolved oxygen and increases the evaporation process.
2. The deposition of sludge reduces the clarity of water and enhances the activities of the microbes compromising the quality of water.
3. Photosynthesis process increases the O_2 in groundwater in the daylight, but it reduces at night.
4. Time passage is also an important contributing factor as flowing water has more oxygen concentration and better purification than stagnant water.

Biochemical Oxygen Demand (BOD)

Biochemical Oxygen Demand (BOD) is the amount of Dissolved Oxygen (DO) by aerobic biological organisms to split the organic substance present in each water sample at a specific temperature over a described time. The BOD value is usually expressed in the milligram of oxygen consumed per liter of water sample during five days of incubation at 20 ^{0}C and often used as an indicative for degree of organic pollution in water. The biochemical oxygen demand used as an instrument for the effectiveness of wastewater treatment

Table 2: Common diseases and their causative biological agents (Van der Perk 2013)

Sr#	Diseases	Causative agents	General Symptoms
Bacterial diseases			
1	Botulism	Clostridium botulinum	Blur vision, dry mouth, difficulty swallowing, muscular weakness, vomiting, diarrhea
2	Cholera	Vibrio Cholera	Watery diarrhea, vomiting, cramps, rapid pulse, nosebleed, hypovolemic shock
3	Dysentery	Shigella, Salmonella	Bloody stool, vomiting of blood
4	Typhoid	Salmonella typhi, Salmonella para typhi	High-grade fever, loss of appetite
5	Campylobacteriosis	Campylobacter jejuni	Dynasty-like symptoms with high-grade fever.
6	Legionellosis	Legionella pneumophila	Diarrhea, nausea, vomiting, nose bleeds, hypovolemic shock,
7	Leptospirosis	Leptospira	In the first phase flu-like symptoms, in the second meningitis, and liver damage.
8	Salmonellosis	Salmonella	Diarrhea, vomiting, and abdominal cramps
Viral diseases			
9	Hepatitis A	Hepatitis A virus	Fatigue, fever, abdominal pain, nausea, weight loss, itching, jaundice, depression, and malaise-like symptoms. Only acute phase
10	Hepatitis E	Hepatitis E virus	Fever, malaise, dark urine, clay-colored stool, loss of appetite, and joint pain.
11	Poliomyelitis	Poliovirus	Headache, fever, spasmodic muscles
	Protozoal diseases		
12	Amoebiasis	Entamoeba histolytica	Abdominal pain, weight loss, diarrhea, bloating, fever
13	Cryptosporidiosis	Cryptosporidium parvum	Flu symptoms, watery diarrhea, loss of appetite, nausea, bloating, and increased gas.
14	Cyclosporiasis	Cyclospora cayetanesis	Cramps, nausea, flu, muscle ache.
15	Giardiasis	Giardia lamblia	Abdominal discomfort, bloating, and diarrhea
16	Naeglerias is	Naegleria fowleri	Headache, hallucination, light sensitivity, fatigue, weight loss, coma
17	Microsporidisis	Microsporidia	Diarrhea and wasting in an immunocompromised individual
	Algal diseases		
18	Desmodesmus infection	Desmodesmus armatus	Can enter in an open wound, a fungal infection-like appearance
	Parasitic worms		
19	Dracunculiasis	Dracunculus mimesis	Slight fever, rash itchy, dizziness, vomiting, and diarrhea

plants (Kilvington et al. 2004). Most of the moderately contaminated streams have a BOD value between 1 to 8 ppm. Ideally, BOD value is decided from the undiluted river water sample in which the use of oxygen increases with increase in temperature (Asim et al. 2012).

Chemical Oxygen Demand

Chemical oxygen demand is the measure of the amount of oxygen that can be spent by reactions in a measured solution. It could express in the mass of oxygen over the volume of solution which is milligram per liter (mg/L). A COD test is used to quantify the number of organic matters in the water sample. The most common application of COD is quantifying the number of oxidizable pollutants found in the surface water (Kelly 1976).

Water Quality Objectives

Uncontaminated surface water is still not pure when compared with the controls such as rainwater or distilled water. It contains dissolved gases and minerals as well as a small amount of organic matter. The characteristics of surface water quality have been mentioned in Table 3 (Brick et al. 2004).

These characteristics of water are usually considered under the category of contamination. In addition, its ability to assimilate the added pollutants must consider of its present degree of impurity, its volume, and its buffering capabilities. Some other contaminants such as calcium, manganese, iron, and sulfate are essential for aquatic life as well as for human life but pure or distilled water does not contain these elements and these are only present in lakes, rivers, and stream water. Cummins (1972) classified unpolluted and polluted water as rivers, lakes, streams, and the distilled water. The classification now are considered as general water quality standards (Centi and Perathoner 2003). The allowable limit of contaminants in the freshwater sample is enlisted in Table 4.

Generally, there are five standards of water used for multiple purposes, including;

1. Drinking purpose without any treatment
2. Drinking purposes after complete treatment
3. Bathing
4. Fishing
5. Agricultural/industrial cooling

Each standard has specific qualities and characteristics which could be used as comparable water quality standards (Hagedorn et al. 1981).

Quality Standards for Class A: Standard A is used for drinking purposes, culinary and food processing. Water treatments include coagulation, sedimentation, filtration, and disinfection. Dissolved oxygen should not be less than 5 ppm. The range of pH should be between 6.5 to 8.5. There should be no toxic waste, oils, harmful substances and heated liquids(Yates 1985).

Table 3: Characteristics of Surface Freshwater

pH	6.8
Dissolved oxygen	9.0 ppm
Temperature	13 ^{0}C
Color	Colorless
Turbidity	5 ppm
BOD (20 ^{0}C, 5-days)	1.2 ppm
Hardness	225 ppm as CaCO$_3$
Chloride	10 ppm as Cl
Total solids	500 ppm

Table 4: Allowable contamination in freshwater (Centi and Perathoner 2003)

Contaminants	Allowable limits in the freshwater
pH	6.0- 8.5
Temperature	20 C
Dissolved oxygen per ml	4.0
Turbidity	29
Color	No specific criteria
Toxic substances	Nil
Biochemical oxygen demand	Limited by D. O
Arsenic	0.05 mg/l
Detergents	0.5 mg/l
Nutrients	Negative
Oils and gases	5.0 mg/l
Dissolved solids	0.001 mg/l

Quality Standards for Class B: Class B water is used for bathing and household washing. And could be harmful for drinking purpose. The specifications include no sludge deposits, absence of settleable solids, industrial waste and toxic waste, and other harmful substances. The range of pH should be between 6 to 8.5 and dissolved oxygen should not be less than 5 ppm (Vilela et al. 2018).

Quality Standards for Class C: It is best used for fishing, freshwater lives, and sometimes bathing. Visible and attributable sewage, plastics, harmful waste substances, oils, gases, heated liquids, and synthetic colors should not be present. For trout water, pH should not exceed the limit above 8.5 and below 6. The dissolved oxygen level of above 5 ppm is important for fisheries (Vilela et al. 2018).

Quality Standards for Class D: It is best used for agriculture, and industrial process, but not for food industries. Its pH limit is between 6-9 and dissolved oxygen should not be less than 3.0 ppm. It holds a little number of toxic elements, oils, gases, and waste substances (Vilela et al. 2018).

Contaminants in Water

The community faces major water contamination, when it looks to expand its water supply. This is true in dwindling freshwater and dependable sources such as municipalities and housing societies. The water supply has the considerable level of contaminants. In 1962 the United States Public Health Services revised the standards of drinking water due to increased contamination as been mentioned in Table 5.

The composition of surface and groundwater is dependent on the natural factors including geological, hydrological, biological, topographic, and metrological factors. There is a minor contribution of seasonal variations, weather changes, and water levels as well. There are also natural variations at a larger scale that involve human interventions. Some of these effects are hydrological changes, housing societies, building dams, draining of wetland, division of flow, pollutants from industries, and household activities. Urbanization is also considered as a major contributor (Bove et al. 1995).

Water Purification Treatments

1. Reserve Osmosis Water Filtration

Reserve osmosis is the process of pumping water down through the semi-permeable membrane. When water pushed against the reserve osmosis membrane surface, the dissolved material repelled, while the water molecules dispersed through the membrane and pure water received on the other side. This is a popular method for the reduction of pollutants. Reserve osmosis removes the major contaminants (Bedient et al. 1994).The percentages of various contaminants that can be removed by reverse osmosis has been mentioned in Table 6.

2. Ultraviolet Water Sterilization and Filtration

The UV rays from sunlight kills the microorganisms. Although it is low-intensity rays, but 254 nanometer frequency can penetrate and kills the microbes. This is referred as the germicidal spectrum. The UV lamps used in water treatment specifically designed to treat water with high-frequency rays. 99.9 % of pathogenic bacteria killed by using this process including (Sharma and Bhattacharya 2017):

i) Coliform bacteria
ii) Salmonella
iii) Typhus
iv) E. coli
v) Viruses
vi) Giardia
vii) Polio
viii) Cryptosyrodium
ix) Hepatitis
x) Cholera

1. Tap Water Filtration

This is a process in which water passes through the system that includes one or more filters for the purpose of removing impurities, turbidity, odor and chemicals such as chlorine.

Table 5: US Public Health Services Drinking water standards (Singh and Steinnes 2020)

Sr #	Contaminants	Allowable concentration (mg/l)
1	Alkyl benzene sulfonate	0.5
2	Arsenic	0.01
3	Chlorides	250.0
4	Copper	1.0
5	Chloroform extract	0.2
6	cyanide	0.01
7	Fluoride	1.0
8	Iron	0.3
9	Manganese	0.05
10	Nitrate	45.0
11	Phenols	0.001
12	Sulfates	250.0
13	Dissolved solids	500
14	Zinc	5.0
15	Lead	0.05
16	Selenium	0.01
17	Silver	0.05
18	Radium 226	3 µ µ c /l
19	Strontium ninety	10 µ µ c/l
20	Gross beta radiation	1000 µ µ c
21	Bacteria (coliform)	10%
22	Turbidity	Five units
23	Color	Fifteen units
24	Threshold odor number	3

Table 6: Contaminants removed through reserve osmosis (Sharma 2021)

Contaminants	Percentages
Lead	85-92%
Arsenic	92-96 %
Pesticides	97-99%
Fluorides	85-92%
Chlorine	96-98%
Barium	95-98%
Cyanides	84-92%
Sodium	84-94%

The design of these filters is just like loose media tank-type systems or cartridge devices. Other catalyst systems are also used to oxidize the contaminated agents, which can be separated by using oxidizing filters (Brennan 2008).

2. Distillation

Distilled water is the purified water passes from one or more evaporation systems through the heated process, and condensation cycles and has no solid particles (O'Neill et al. 2003).

Water Treatment Steps in the Treatment Plant

Coagulation: The first step in water management is coagulation in which chemicals with a positive charge are attached with the water molecule. These positive charges neutralize the negative charges present in the dirt and other dissolved particles. In this process, the particles bind together to form larger particles, that are easily filtered through the filtration process. Common chemicals used include aluminum, iron, and salts.

1. Flocculation: It is the process of gentle mixing of water to separate larger and heavier particles called flocs.
2. Sedimentation: During this step, solid particles including flocs are settled down as heavier particles and separated (Tariq et al. 2020).
3. Filtration: After sedimentation clear liquid passes through the distinct size pores to filter the remaining contents (Iqbal 2010).
4. Disinfection: Filtered water passes through the disinfection process and during this process, various chemicals including chlorine, chloramine and chloride oxides are used to kill bacteria and other pathogenic microorganisms (Schweitzer and Noblet 2018).

Global Water Crisis and Future Perspectives

Across the world, water reached its scarcity level and human activities aggravate freshwater pollution. The scarcity of freshwater potentially limits food production, ecosystem functioning, and supply of food (Khan et al. 2012). The ecological destruction describes the crisis throughout the globe including Pakistan, India, China, Jordan, Turkey and Australia. First, the water is accessed by multiple stakeholders who have different quality and timing for needs (Soharwardi et al. 2021). The perspective of a single stakeholder about water vulnerability and the unsustainability of water supply is inadequate. In the industrialized countries, the population growing rapidly increases the water demand, thus the stakeholders seeing for reallocation of water resources. Secondly, there is a range of time frames and concerns. Both long-term decline and short-term water crisis are related to supply variability and turn to chronic scarcity of water. Finding short-term and long-term crisis dynamics could be helpful to overcome the scarcity (Pye and Patrick 1983).

Causes of the Water Crisis in Pakistan

There are a lot of causes responsible for water crisis, in which man-made and natural contributes equally. It includes 1) rapid population growth 2) density and urbanization 3) lack of law enforcement 4) misguided agricultural development and polices 5) high vulnerability to climate 6) lack of proper management especially flooding 7) lack of infrastructure such as Dams. Human activities and water wasting at larger level induced the crisis. In Pakistan there is no law enforcement to control the factors associated with human activities (Hanjra and Qureshi 2010).

Consequences of Water Scarcity

All the contributing causative agents leads towards unmanageable consequences. Shortage of water is the major concern of 20th century. The important consequences of water scarcity includes; 1) Lack of access to drinking water 2) Hunger/shortage of food 3) Diseases 4) Inappropriate sanitation 5) Poverty 6) Migration 7) Destruction of habitats and 8) Loss of biodiversity (Hedden and Cilliers 2014).

Preventive Measures/Solutions

There are different measures or solutions to save water and prevent water shortage which includes 1) Save water 2) Mass-level awareness programs 3) Education 4) Water recycling 5) Advance technologies related to water conservation 6) Improve practice of irrigation 7) Less use of chemicals in the farms 8) Improve sewage system 9) Good water distribution infrastructure and 10) Support clean water initiatives (Nabi et al. 2019).

Conclusion

Water is the basic need for life. The water crisis and less availability of clean water for drinking purpose is a major problem across the globe. Bacterial, viral, fungal, and protozoal diseases enhance the burden of disease and mortality rate. The accessibility of pure water by using different purification methods is important in urban as well as in rural population. Agricultural management and law enforcement are the important steps as a preventive measure for water scarcity.

REFERENCES

Asim M et al., 2012. Socio Economic Impact of Water Crisis on Agrarian Community in District Faisalabad, Pakistan. Mediterranean Journal of Social Sciences 3: 235.

Bedient PB et al., 1994. Ground water contamination: transport and remediation., Prentice-Hall International, Inc.

Blanchoud H et al., 2007. Contribution by urban and agricultural pesticide uses to water contamination at the scale of the Marne watershed. Science of the Total Environment 375: 168–179.

Boulding JR and Ginn JS, 2016. Practical handbook of soil, vadose zone, and ground-water contamination: assessment, prevention, and remediation, CRC Press.

Bove FJ et al., 1995. Public drinking water contamination and birth outcomes. American Journal of Epidemiology 141: 850–862.

Brennan JF, 2008. The China-India-Pakistan water crisis: prospects for interstate conflict, Naval Postgraduate School Monterey CA.

Brick T et al., 2004. Water contamination in urban south India: household storage practices and their implications for water safety and enteric infections. International Journal of Hygiene and Environmental Health 207: 473–480.

Centi G and Perathoner S, 2003. Remediation of water contamination using catalytic technologies. Applied Catalysis B: Environmental 41: 15–29.

Clement KK and Julius MN, 2012. Well water contamination by pit latrines: a case study of Langas. International Journal of Water Resources and Environmental Engineering 4: 35–43.

Hagedorn C et al., 1981. The potential for ground water contamination from septic effluents. Journal of Environmental Quality 10: 1–8.

Hanjra MA and Qureshi ME, 2010. Global water crisis and future food security in an era of climate change. Food Policy 35: 365–377.

Hedden S and Cilliers J, 2014. Parched prospects-the emerging water crisis in South Africa. Proceedings of Institute for Security Studies Papers; 1 September 2014, pp: 16.

Iqbal AR, 2010. Water Shortage in Pakistan-A Crisis around the Corner. The Journal of Governance and Public Policy 2: 1-13.

De Jong R et al., 2009. Risk of water contamination by nitrogen in Canada as estimated by the IROWC-N model. Journal of Environmental Management 90: 3169–3181.

Kelly WE, 1976. Geoelectric sounding for delineating ground-water contamination. Groundwater 14: 6–10.

Khan AN et al., 2012. Energy crisis in Pakistan: causes and consequences.

Kilvington S et al., 2004. Acanthamoeba keratitis: the role of domestic tap water contamination in the United Kingdom. Investigative Ophthalmology and Visual Science 45: 165-169.

Nabi G et al., 2019. The crisis of water shortage and pollution in Pakistan: risk to public health, biodiversity, and ecosystem. Environmental Science and Pollution Research 26: 10443-10445.

O'Neill MS et al., 2003. Health, wealth, and air pollution: advancing theory and methods. Environmental Health Perspectives 111: 1861–1870.

Van der Perk M, 2013. Soil and Water Contamination 2nd Edition (Special Sale Only): From Molecular to Catchment Scale, CRC press.

Pye VI and Patrick R, 1983. Ground water contamination in the United States. Science 221: 713–718.

Robertson WD et al., 1991. Ground-water contamination from two small septic systems on sand aquifers. Groundwater 29: 82-92.

Schweitzer L and Noblet J, 2018. Water contamination and pollution. In: Green Chemistry, Elsevier, pp: 261–290.

Seiler RL et al., 1999. Caffeine and pharmaceuticals as indicators of waste water contamination in wells. Groundwater 37: 405-410.

Sharma R, 2021. Examination of incidence, mortality and disability-adjusted life years and risk factors of breast cancer in 49 Asian countries, 1990–2019: estimates from Global Burden of Disease Study 2019. Japanese Journal of Clinical Oncology 51: 826–835.

Sharma S and Bhattacharya A, 2017. Drinking water contamination and treatment techniques. Applied Water Science 7: 1043–1067.

Singh BR and Steinnes E, 2020. Soil and water contamination by heavy metals. In: Soil Processes and Water Quality, CRC Press, pp: 233–271.

Soharwardi MA et al., 2021. Impact of water crisis on food production in Pakistan: a time-series analysis. International Journal of Agricultural Extension 9: 429–437.

Tariq MAUR et al., 2020. An engineering perspective of water sharing issues in Pakistan. Water 12: 477.

Theodore L, 1990. Air pollution control and waste incineration for hospitals and other medical facilities.

Vilela CLS et al., 2018. Water contamination by endocrine disruptors: Impacts, microbiological aspects and trends for environmental protection. Environmental Pollution 235: 546-559.

Yates MV, 1985. Septic tank density and ground-water contamination. Groundwater 23: 586–591.

Impact of Emerging Pollutants on a Health Triad: Environment, Animals and Humans

AUTHORS DETAIL

Pablo Antonio Moreno-Pérez[1], Gauddy Lizeth Manzanares-Leal[1], Miguel Ángel Karam Calderon[1], Yazmín Castillo Sánchez[1] and Ninfa Ramírez-Durán[1]*

[1]Facultad de Medicina, Universidad Autónoma del Estado de México, Toluca, Estado de México
*Corresponding author: ninfard@hotmail.com

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INTRODUCTION

Emerging pollutants (EP) are the compounds of anthropogenic origin that usually do not screened in the environment (Geissen et al. 2015; Teodosiu et al. 2018). EP in the environment is influenced by several factors, such as population growth, which has generated a high demand for "hazardous" chemicals for health, approximately more than 220 million tons (https://ec.europa.eu/eurostat/). EP include those of pharmaceutical origin (FEP), synthetic or natural chemical substances used as commercial prescription drugs for therapeutic and veterinary use to diagnose, cure, treat or prevent diseases in humans and animals. (WHO 2012; Nyagah et al. 2020). FEP include many analgesics, antidiabetics, antibiotics, antidepressants, steroid antihypertensives and stimulants (Schwartz et al. 2021; Turcios et al. 2021). The subministering of FEP is regulated for patient safety, but the side effect of any drug on the environment lacks regulation (Anchique et al. 2021). In general, estimated three-quarters of polluting industrial emissions are discharged into the environment without pretreatment (Vasilachi et al. 2021). Due to this situation, PEFs and their metabolites are released into the environment through treatment plants (Massima et al. 2021) and human sanitary discharges without prior treatment. The above generates a threat to the environment since chronic exposure to various pharmaceutical substances, the increase in the concentration of FEPs as they accumulate in the environment and the great variety of substances that can be found, coupled with their low biodegradability and high persistence, allows their bioaccumulation in various systems, from the lowest trophic levels to humans (Fonseca et al. 2020; Turcios et al. 2021). Because of the evidence of various FEP in the environment, intensive research on their fate and risk has generated significant interest (Mulkiewicz et al. 2021).

Impact of Emerging Pollutants on the Environment

In 2019, the global pharmaceuticals manufacturing market was estimated to be over $320 trillion (320 billion, with a compound annual growth rate of over 13% from 2020 to 2027 (Grand View Research 2020). Approximately 4000 active pharmaceutical products are manufactured and incorporated into thousands of products available in the market (Daughton 2014). The pharmaceutical product cycle consists of three main stages: manufacture, consumption, and disposal (Kusturica et al. 2020). When the manufacturing process is completed, pharmaceuticals are distributed in multiple presentations, such as tablets, capsules, and liquid formulations (Dunn et al. 2010). Once orally ingested by the body (human or animal), 30-90% is not entirely metabolized and is excreted as an active substance (Nyagah et al. 2020; O'Flynn et al. 2021), mainly through urine (70% on average) and feces (30%) (Abdel-Shafy and Mohamed-Mansour 2013; Hassan et al. 2019).

Pharmaceutical FPs can integrate into the environment through the manufacturing process, disposed or unused products, excretion by humans and animals, wastewater discharges, livestock husbandry, and leached landfill sites (Kleywegt et al. 2019; Lam et al. 2021). Although the concentrations of FEP found in the environment, have been in the ng/L and g/L ranges (Tran 2013; Ahmed et al. 2017), yet these can cause ecological disturbances (Belhaj et al. 2015), as well as adverse effects on human health. Due to the evidence of their presence in the environment, interest in their research has increased in the scientific community in recent decades (Turcios et al. 2021).

Impact of Emerging Pollutants on Animals

The administration of drugs to animals is a strategy to prevent and combat disease and maintain optimal health (CDDEP 2021). In 2010 alone, livestock consumed more than 63,000 tons of antimicrobial drugs worldwide, which will be more than 100,000 tons by 2030 (Van Boeckel et al. 2015). However, drugs administered to animals are not fully metabolized (Zhao et al. 2010). Numerous studies have

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reported the presence of drugs such as fluoroquinolones, antibiotics, sulfonamides, and tetracyclines in animal manure samples (Qiao et al. 2012; Li et al. 2013; Hou et al. 2015; Van Epps and Blaney 2016); which may pose a threat to animal species. The transfer of drugs through food chains may interfere with other species ecological systems (Chopra and Kumar 2018).

The negative impact of PEFs on the animal body has been reported, for example, in the decline of vulture populations (*Gyps indicus, Gyps bengalensis, Gyps tenuirostris*) in countries such as Bangladesh, India, Nepal, Pakistan and Switzerland, due to poisoning with antibiotics and non-steroidal anti-inflammatory drugs (Prakash et al. 2003; Oaks et al. 2004; Swan et al. 2016). Another example is the amphipod crustacean Gammarus locusta which, exposed to simvastatin, alters its reproduction and growth (Neuparth et al. 2014). In rainbow trout (*Oncorhynchus mykiss*), this same drug causes hepatic cytotoxicity, metabolic inhibition, and cell membrane loss (Ellesat et al. 2020).

On the other hand, carbamazepine inhibits molting and growth in the crab *Eriocheir sinensis* (Chen et al. 2019). It causes malformations during embryonic development in the Mediterranean mussel *Mytilus galloprovincialis* (Franzellitti 2019), as well as alterations in motility and behavior in embryos of the zebrafish, *Danio rerio* (Weichert et al. 2017). Diclofenac, a non-steroidal anti-inflammatory drug, can cause oxidative stress and affect testosterone levels in wolf fish *Hoplias malabaricus* (Guiloski et al. 2015); cytological changes in liver, kidneys, and gills of *O. mykiss* (Schwaiger et al. 2004); lower hematocrit levels in brown trout *Salmo trutta* (Hoeger et al. 2005); toxic effects in catfish *Rhamdia quelen* (Ribas et al. 2017); ragworm, *Hediste diversicolo* and sole fish *Solea senegalensis* (Nunes et al. 2020); in tilapia *Oreochromis niloticus* (Gröner et al. 2017) and the fish Corvina, *Argyrosomus regius* (Duarte et al. 2020).

Impact of Emerging Pollutants on Humans

The availability of clean water is indispensable for human health. While considering the population and industrial growth worldwide, the need for clean water is increasing (Tortajada 2020; Lam et al. 2021). The presence of FEP threatens the supply and availability of freshwater. Various research suggests that 70% of FEP are from domestic water and 30% from industrial waste, which is discharged directly into rivers without treatment (Bunke et al. 2019; Tang et al. 2019). Even in the case of treated wastewater, the accumulation of FP does not allow its reuse, limiting the under-supply of drinking water (Massima et al. 2021). The presence of PEFs has been described in freshwater and drinking water sources, finding antibiotics and non-steroidal anti-inflammatory drugs (Fernandes et al. 2020; Khan et al. 2020; Ngqwala and Muchesa 2020). These accumulate directly in water sources, causing adverse effects on microorganisms and aquatic animals through bioaccumulation in food chains and favoring antibiotic resistance in bacteria, leading to a threat for health and safety (Hassoun-Kheir et al. 2020; Wang 2020).

Studies conducted by Savin et al. (2021) and León-Aguirre et al. (2019) in swine facilities for meat intended for human consumption found that *E. coli* bacteria presented resistance to the antibiotic's ciprofloxacin and piperacillin. They also found enrofloxacin, oxytetracycline, and sulfamethoxazole in wastewater treated by biodigesters.

The constant accumulation and under-supply of antibiotics allow the generation of resistance genes. Liang et al. (2021) identified the genes APH(3′)-IIIa, APH(6)-Id, APH(3")-Ib; OXA-347; ermF, msrE, cfrA and tetQ, tet36, tetX, tetM (resistant to aminoglycoside, β-lactam, macrolide-lincosamide-streptogramin, tetracycline respectively) from China. For their part, in swine wastewater, Suzuki et al. (2021) found the antibiotics lincomycin and tetracyclines also detected the presence of the resistance genes sul1, sul2, sul3, and tet(M), suggesting that, even if the use of antibiotics is suspended, the resistance genes remain in the environment for an extended period. The exposure of microorganisms to antibiotics can favor the generation of resistance to different antibiotics through mechanisms such as impermeable barriers, efflux pumps, drug inactivation, and mutational resistance (Allen et al. 2010). A Study by Andersson and Hughes 2014 reveal that even non-lethal levels of antibiotics in the environment can exacerbate the selection and enrichment of resistance genes.

General Information on the Removal of Emerging Pollutants

Unlike conventional contaminants, the removal of PE presents characteristics that complicate its removal. They are polar molecules; the pH of the medium affects their properties and can present variations in structure, form, and functionality. In addition, once consumed, absorbed, and eliminated, these can present changes in their chemical structure due to the previous metabolic process (Rivera-Utrilla et al. 2013). The sum of all these characteristics and the presence of different EP in the same environments makes it more complex to understand all interactions, which are not evident today.

The strategy of eliminating or removing FEP from the environment started because the natural attenuation of these compounds based on physical, chemical, and biological processes is insufficient due to the many xenobiotic compounds released. Processes for the elimination or removal of EP generally involve biological and physicochemical treatments. According to Liu et al. (2020), biological processes include Activated Sludge treatments based on coagulation, adsorption, and oxidation of sludge; Membrane Bioreactors, a process that combines microbial degradation and membrane separation; Composting based on animal manure; Phytoremediation based on microalgae; and Bacterial Bioremediation. Among the physical and physicochemical processes, there are Membrane Processes, which use porous or non-porous membranes to filter contaminants; Adsorption of mineral surfaces and ion exchange, which uses substrates such as modified natural zeolite; Carbon Adsorption, used as adsorption material; Coagulation, for the removal of non-polar molecules and the use of nanomaterials such as graphene. In addition, the same author mentions chemical oxidation, which can destroy the molecular structure of some pollutants or favor their biodegradability, such as ozone use. Ozone can react with some pollutants giving rise to a series of free radicals or produce some hydroxyl radicals to degrade the pollutants, depending on the acidity or alkalinity. Electrochemical oxidation is based on oxidation by an electrical voltage; catalysis, which includes processes such as photolysis and photocatalysis; and treatment technologies.

Although all contaminant removal treatments have advantages, they also have disadvantages. Activated sludge can be affected by temperature and pollutant types (Liu et al. 2020); membrane bioreactors by the cost of membrane materials, sludge concentration, solids retention time and organic loading (Zhen et al. 2019); composting can be influenced by temperature; ozone is only effective on some pollutants, plus it is unable to fully oxidize or mineralize them (Liu et al. 2020). Membrane processes are hindered by membrane flux, pore size, hydrophobicity, and molecular weight of the pollutant, and adsorption from mineral surfaces and ion exchange present low capacity and poor selectivity. Carbon adsorption depends on the surface area, pore structure, and functional surface (Xing et al. 2019; Zhang et al. 2019); electrochemical oxidation quickly produces degradation intermediates and electrode deactivation (Tasca et al. 2019) and catalysis is influenced by the pH value of the solution, type of light source and own characteristics of the catalysts (Carena et al. 2019). The results of the investigations have shown that the removal of EP is generally not completely efficient.

Removal of Emerging Pollutants from Pharmaceuticals

The main treatments to remove or eliminate FEP include collection for subsequent incineration, collection in ordinary dumpsters, and discharge into the sewage system for subsequent wastewater treatment (Bu et al. 2020). These treatments have advantages and disadvantages; incineration presents destruction and a significant reduction of waste volume (Ghasemi and Yusuff 2016; Trinh et al. 2020) but can release heavy metals into the atmosphere (Sabiha-Javied et al. 2008); in addition to the cost associated with the design and construction of these facilities. The collection in ordinary dumpsters uses specific sites to deposit waste and isolate it from the surrounding environment (Narayana 2009). However, due to the increased pharmaceutical production and volume disposed of, the designated areas are insufficient, so the drugs are leached. Previous studies have detected a complex mixture of contaminants, including FEP, in multiple landfills in 100 to 1,000,000 ng/L (Masoner 2014). The wastewater treatment process has proven to be efficient, mainly for removing conventional contaminants, such as biodegradables, organic matter, and nutrients, but it is not efficient for removing pharmaceuticals (Kümmerer 2008; Sim et al. 2010).

Conclusion

The process of manufacturing, distribution, consumption, and disposal of FEP is a polluting phenomenon for the environment, animals, and humans. The complex mixture of diverse FEP threatens the environmental impact in diverse ecosystems. Some of the alternatives to diminish this impact on the health triad are to initiate the process of regulating FEP in the environment, establish control, management, and distribution laws, as well as permanent monitoring of the diverse ecosystems related to the presence of FEP, promote international research in remediation processes with new technologies, as well as the use of common treatment methods.

REFERENCES

Abdel-Shafy HI and Mohamed-Mansour MS, 2013. Issue of pharmaceutical compounds in water and wastewater: Sources, impact and elimination. Egyptian Journal of Chemistry 56 (5–6): 449–471.

Ahmed MB et al., 2017. Progress in the Biological and Chemical Treatment Technologies for Emerging Contaminant Removal from Wastewater: A Critical Review. Journal of Hazardous Materials 323: 274–298.

Allen HK et al., 2010. Call of the wild: antibiotic resistance genes in natural environments. Nature Reviews Microbiology 8: 251–259.

Anchique L et al., 2021. Predicting the Adsorption of Amoxicillin and Ibuprofen on Chitosan and Graphene Oxide Materials: A Density Functional Theory Study. Polymers 13: 1620.

Andersson DI and Hughes D, 2014. Microbiological effects of sublethal levels of antibiotics. Nature Reviews Microbiology 12: 465–478.

Belhaj D et al., 2015. Fate of Selected Estrogenic Hormones in an Urban Sewage Treatment Plant in Tunisia (North Africa). Science of The Total Environment 505: 154–160.

Bu Q, 2020. Is disposal of unused pharmaceuticals as municipal solid waste by landfilling a good option? A case study in China. Bulletin of Environmental Contamination and Toxicology 105: 784–789.

Bunke D et al., 2019. Developments in society and implications for emerging pollutants in the aquatic environment. Environmental Sciences Europe 31: 1–17.

Carena L et al., 2019. Environmental photodegradation of emerging contaminants: A reexamination of the importance of triplet-sensitised processes, based on the use of 4-carboxybenzophenone as proxy for the chromophoric dissolved organic matter. Chemosphere 237: 124476.

CDDEP, 2021. The State of the World's Antibiotics 2021: a Global Analysis of Antimicrobial Resistance and its Drivers.

Chen H et al., 2019. Carbamazepine disrupts molting hormone signaling and inhibits molting and growth of Eriocheir sinensis at environmentally relevant concentrations. Aquatic Toxicology 208: 38–145.

Chopra S and Kumar D, 2018. Pharmaceuticals and Personal Care Products (PPCPs) as Emerging Environmental Pollutants: Toxicity and Risk Assessment. In: Gahlawat, Advances in Animal Biotechnology and its Applications. Springer, Singapore.

Daughton CG, 2014. Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs. Science of The Total Environment 493: 392–404.

Duarte IA et al., 2020. Depressed, hypertense and sore: longterm effects of fluoxetine, propranolol and diclofenac exposure in a top predator fish. Science of The Total Environment 712: 136564.

Dunn PJ et al., 2010. Green chemistry in the pharmaceutical industry. In: Dunn, P.J., Wells, A.S., Williams, M.T. (Eds.), Green Chemistry in the Pharmaceutical Industry. Wiley-VCH Verlag GmbH & Co. KGaA.

Ellesat KS et al., 2020. Cytotoxicity of atorvastatin and simvastatin on primary rainbow trout (Oncorhynchus mykiss) hepatocytes. Toxicolgy In Vitro 24: 1610–1618.

Fernandes MJ et al., 2020. Antibiotics and antidepressants occurrence in surface waters and sediments collected in the north of Portugal. Chemosphere 239.

Fonseca VF et al., 2020. Roving Pharmacies: Modelling the Dispersion of Pharmaceutical Contamination in Estuaries. Ecological Indicators 115: 106437.

Franzellitti S, 2019. Microplastic exposure and effects in aquatic organisms: A physiological perspective. Environmental Toxicology and Pharmacology 68: 37–51.

Geissen V et al., 2015. Emerging pollutants in the environment: A challenge for water resource management. International Soil and Water Conservation Research 3: 57–65.

Ghasemi MK and Yusuff RBM, 2016. Advantages and disadvantages of healthcare waste treatment and disposal alternatives: Malaysian scenario. Polish Journal of Environmental Studies 25: 17–25.

Grand View Research, 2020. Pharmaceutical Manufacturing Market Size, Share & Trends Analysis Report By Drug Development Type, By Formulation, By Route Of Administration, By Therapy Area, By Prescription, By Age Group, And Segment Forecasts, 2020-2027.

Gröner F et al., 2017. Chronic diclofenac exposure affects gill integrity and pituitary gene expression and displays estrogenic activity in nile tilapia (Oreochromis niloticus). Chemosphere 166: 473–481.

Guiloski IC et al., 2015. Effects of trophic exposure to dexamethasone and diclofenac in freshwater fish. Ecotoxicology and Environmental Safety 114: 204–211.

Hassan SSM et al., 2019. Removal of pharmaceutical compounds from urine via chemical coagulation by green synthesized ZnO-nanoparticles followed by microfiltration for safe reuse. Arabian Journal of Chemistry 12: 4074–4083.

Hassoun-Kheir N et al., 2020. Comparison of antibiotic-resistant bacteria and antibiotic resistance genes abundance in hospital and community wastewater: A systematic review. Science of The Total Environment 743: 140804.

Hoeger B et al., 2005. Water-borne diclofenac affects kidney and gill integrity and selected immune parameters in brown trout (Salmo trutta f. fario). Aquatic Toxicology 75: 53–64.

Hou J et al., 2015. Occurrence and distribution of sulfonamides, tetracyclines, quinolones, macrolides, and nitrofurans in livestock manure and amended soils of Northern China. Environmental Science and Pollution Research 22: 4545–4554.

Khan HK et al., 2020. Fate and toxicity of pharmaceuticals in water environment: An insight on their occurrence in South Asia. Journal of Environmental Management 271.

Kleywegt S et al., 2019. Environmental loadings of active pharmaceutical ingredients from manufacturing facilities in Canada. Science of the Total Environment 646: 257– 264.

Kümmerer K, 2008. Pharmaceuticals in the Environment: Source, Fate, Effects and Risk K. Kümmerer (ed.); Third, Vol. 53, Issue 9). Springer-Verlag Berlin Heidelberg.

Kusturica MP et al., 2020. Consumer willingness to pay for a pharmaceutical disposal program in Serbia: a double hurdle modeling approach. Waste Management 104: 246–253.

Lam VT et al., 2021. Facile Fabrication of Novel NiFe2O4@Carbon Composites for Enhanced Adsorption of Emergent Antibiotics. Materials 14: 6710.

León-Aguirre K et al., 2019. A Rapid and Green Method for the Determination of Veterinary Pharmaceuticals in Swine Wastewater by Fluorescence Spectrophotometry. Bulletin of Environmental Contamination and Toxicology 103: 610-616.

Li YX et al., 2013. The residues and environmental risks of multiple veterinary antibiotics in animal faeces. Environmental Monitoring and Assessment 185: 2211–2220.

Liang C et al., 2021. Removal of antibiotic resistance genes from swine wastewater by membrane filtration treatment. Ecotoxicology and Environmental Safety 2010.

Liu B et al., 2020. Emerging pollutants—Part II: Treatment. Water Environment Research 92: 1603– 1617.

Masoner JR, 2014. Contaminants of emerging concern in fresh leachate from landfills in the conterminous United States. Environmental Science: Processes and Impacts 16: 2335–2354.

Massima ES et al., 2021. Removal of Pharmaceutical Residues fromWater andWastewater Using Dielectric Barrier Discharge Methods—A Review. International Journal of Environmental Research and Public Health 18: 1683.

Mulkiewicz E et al., 2021. Metabolism of non-steroidal anti-inflammatory drugs by non-target wild-living organisms. Science of The Total Environment 791: 148251.

Narayana T, 2009. Municipal solid waste management in India: From waste disposal to recovery of resources? Waste Manager 29: 1163–1166.

Neuparth T et al., 2014. Hypocholesterolaemic pharmaceutical simvastatin disrupts reproduction and population growth of the amphipod Gammarus locusta at the ng/L range. Aquatic Toxicology 155: 337–347.

Ngqwala NP and Muchesa P, 2020. Occurrence of pharmaceuticals in aquatic environments: A review and potential impacts in South Africa. South African Journal of Science 116.

Nunes B et al., 2020. Toxic effects of environmentally realistic concentrations of diclofenac in organisms from two distinct trophic levels, Hediste diversicolor and Solea senegalensis. Comparative Biochemistry and Physiology Part C 231.

Nyagah DM, 2020. Pharmaceutical Waste: Overview, Management, and Impact of Improper Disposal. Preprints 2020100245.

O'Flynn D et al., 2021. A review of pharmaceutical occurrence and pathways in the aquatic environment in the context of a changing climate and the COVID-19 pandemic. Analytical Methods Journal 13: 575–594.

Oaks JL et al., 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 427: 630–633.

Prakash V et al., 2003. Catastrophic collapse of indian white-backed Gyps bengalensis and long-billed Gyps indicus vulture populations. Biological Conservation 109: 381–390.

Qiao M et al., 2012. Fate of tetracyclines in swine manure of three selected swine farms in China. Journal of Environmental Sciences 24: 1047–1052.

Ribas JLC et al., 2017. Inhibition of immune responses and related proteins in Rhamdia quelen exposed to diclofenac. Environmental Toxicology and Chemistry 36: 2092–2107.

Rivera-Utrilla J et al., 2013. Pharmaceuticals as emerging contaminants and their removal from water. A review. Chemosphere 93: 1268–1287.

Sabiha-Javied et al., 2008. Heavy metal pollution from medical waste incineration at Islamabad and Rawalpindi, Pakistan. Microchemical Journal 90: 77–81.

Savin M et al., 2021. Clinically Relevant Escherichia coli Isolates from Process Waters and Wastewater of Poultry and Pig Slaughterhouses in Germany. Microorganisms 9: 698.

Schwaiger J et al., 2004. Toxic effects of the non-steroidal anti-inflammatory drug diclofenac. Part I: histopathological alterations and bioaccumulation in rainbow trout. Aquatic Toxicology 68: 141–150.

Schwartz H et al., 2021. Pharmaceuticals in source waters of 95 First Nations in Canada. Canadian Journal of Public Health 112: 133–153.

Sim WJ et al., 2010. Occurrence and fate of pharmaceuticals in wastewater treatment plants and rivers in Korea. Environmental Pollution 158: 1938–1947.

Suzuki S et al., 2021. Contamination of antibiotics and sul and tet(M) genes in veterinary wastewater, river, and coastal sea in Thailand. Science of The Total Environment 791: 148423.

Swan GE et al., 2006. Toxicity of diclofenac to Gyps vultures. Biology Letters 2: 279–282.

Tang Y et al., 2019. Emerging pollutants in water environment: Occurrence, monitoring, fate, and risk assessment. Water Environment Research 91: 984–991.

Tasca AL et al., 2019. Electrochemical removal of Terbuthylazine: Boron-Doped Diamond anode coupled with solid polymer electrolyte. Environmental Pollution 251: 285–291.

Teodosiu C et al., 2018. Emerging Pollutants Removal through Advanced Drinking Water Treatment: A Review on Processes and Environmental Performances Assessment. Journal of Cleaner Production 197: 1210–1221.

Tortajada C, 2020. Contributions of recycled wastewater to clean water and sanitation Sustainable Development Goals. NPJ Clean Water 3.

Tran NH, 2013. Insight into Metabolic and Cometabolic Activities of Autotrophic and Heterotrophic Microorganisms in the Biodegradation of Emerging Trace Organic Contaminants. Bioresource Technology 146: 721–731.

Trinh VT et al., 2020. Treatment of medical solid waste using an Air Flow controlled incinerator. Polish Journal of Chemical Technology 22: 29–34.

Turcios AE et al., 2021. Screening of Emerging Pollutants (EPs) in Estuarine Water and Phytoremediation Capacity of Tripolium pannonicum under Controlled Conditions. International Journal of Environmental Research and Public Health 18: 943.

Van Boeckel TP et al., 2015. Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences. Proceedings of the National Academy of Sciences of the United States of America, pp: 5649–5654.

Van Epps A and Blaney L, 2016. Antibiotic residues in animal waste: occurrence and degradation in conventional agricultural waste management practices. Current Pollution Reports 2: 135–155.

Vasilachi IC et al., 2021. Review. Occurrence and fate of emerging pollutants in wáter environmental and options for their removal. Water 13: 181.

Wang J, 2020. Occurrence and fate of antibiotics, antibiotic resistant genes (ARGs) and antibiotic resistant bacteria (ARB) in municipal wastewater treatment plant: An overview. Science of The Total Environment 744: 140997.

Weichert FG et al., 2017. Assessing the ecotoxicity of potentially neurotoxic substances-Evaluation of a behavioural parameter in the embryogenesis of Danio rerio. Chemosphere 186: 43–50.

WHO, 2012. World Health Organization. Pharmaceuticals in Drinking Water. doi: https://doi.org/10.1016/B978-0-444-52272-6.00457-8.

Xing J et al., 2019. Organic matter removal and membrane fouling mitigation during algae-rich surface water treatment by powdered activated carbon adsorption pretreatment: Enhanced by UV and UV/chlorine oxidation. Water Research 159: 283–293.

Zhang P et al., 2019. Microwave-assisted chemical modification method for surface regulation of biochar and its application for estrogen removal. Process Safety and Environment Protection 128: 329–341.

Zhao L et al., 2010. Residues of veterinary antibiotics in manures from feedlot livestock in eight provinces of China. Science of The Total Environment 408: 1069–1075.

Zhen G et al., 2019. Anaerobic membrane bioreactor towards biowaste biorefinery and chemical energy harvest: Recent progress, membrane fouling and future perspectives. Renewable Sustainable Energy Reviews 115: 109392.

7

Power of Positive Human Animal Relationship for Animal Welfare

AUTHORS DETAIL

Faiza Bano[1], Aayesha Riaz[1], Murtaz ul Hassan[1], Sohail Sajid[2], Nazia Rafiq[3] and Muhammad Farooq Iqbal[4]

[1]Department of Parasitology & Microbiology, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan
[2]Department of Parasitology, Faculty of Veterinary Sciences, University of Agriculture, Faisalabad
[3]Department of Anthropology, Faculty of Social Sciences, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan.
[4]Department of livestock production and Management, Faculty of Veterinary and Animal Sciences, Pir Mehr Ali Shah Arid Agriculture University, Rawalpindi, Pakistan
*Corresponding author: sagitarian.vet@gmail.com

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INTRODUCTION

Relationship of human and animal is a significant factor of animal welfare. Domestic animals pursue and enjoy relations and companionship with humans, apart from depending on humans for nutrition. Animals from other classes such as zoo, laboratory and wild animals are also capable to develop positive relations with humans. Operationally human animal relationship can be expressed as animal spatial closeness, relaxation, pleasure, keenness or some other signs of rewarding experience that rise from relations with the human (Hunt et al. 1992). Positive feelings develop for short term through positive human animal relationship and stress flexibility, wellbeing outcomes for animal once or later related to human develop for long term. The relationship between animals and humans is continuous from past and has recognized into different facets associated to fear, appreciation, nutrition, subjugation, transportation, protection, security, company, utilization and fun, etc. Above the last few eras, this affiliation has settled into dissimilar facades which have risen fresh, therapeutic and some hygienic concerns. These concerns have created animal welfare groups, many relations form protest activities in several regions such as civilizations, trade, entertainment and transportation etc (Terlouw et al. 2005).

This chapter briefly discusses about the positive human animal relationship, its assistance, consequences, benefits, effects, domains and measurements of human animal relationship.

Ambition of animal welfare is that animal pass from good and bad experiences throughout its life. It is necessary to provide proper life, physical health and comfort sustaining needs as illustrated in Fig. 1.

Categories of Human and Animal Relationships

Human animal relationship categorized into affiliative relationship, animal assisted intervention and service animals. Animal assisted intervention is further subdivided into animal assisted activities and animal assisted education. Service animal is subdivided into animal assisted therapy (Waiblinger et al. 2006) as shown in Fig. 2.

Assistance of Human Animal Affiliation

Human animal relationship is significant and has long term effects on safety of animals. This affiliation is sometimes life threatening to the animals such as animal production, management, friendship and satisfaction for human. Human animal relationship is stress resilience such as positive relations to housing dogs can decrease cortisol level and unite with physical activity to increase adoptability through walking and patting dogs till fifteen minutes in a week for six weeks, but positive and negative human relations can also influence the dogs sleep (Rybarczyk et al. 2001). Weekly brushing for five minutes to milking heifers assist acclimation to milking routine. Back scratching for five seconds to sows till one week minimized piglet death in sows. This shows that positive relations with humans are advantageous to animal organization as well as animal welfare (Waiblinger et al. 2006). Positive human animal relationship can also defense aversive events such as veterinary examinations and administration involvements for cow, sheep, ostrich and pig by eliminating human related issues that provoke mechanisms. Furthermore, humans can also deliver social maintenance to animals throughout traumatic phase. Social maintenance efficiency can be moderated by the worth of human animal relationship (Hausberger et al. 2008).

Benefits of Human Animal Relationship

Positive relationship with humans gives several benefits as they typically occur every day and it does not need extra assets such as material. Chimpanzees preferred to live in their zoo arena where they can be nearby and notice guests and it represent that animal relations with humans are exciting (Fureix et al. 2009). Humans encourage positive emotive state

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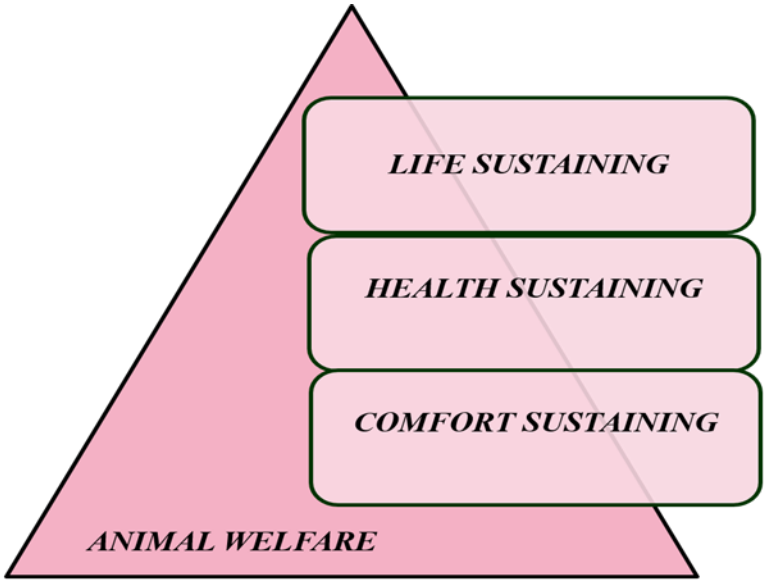

Fig. 1: Animal welfare necessities which include life sustainability, Health sustainability and Comfort sustainability

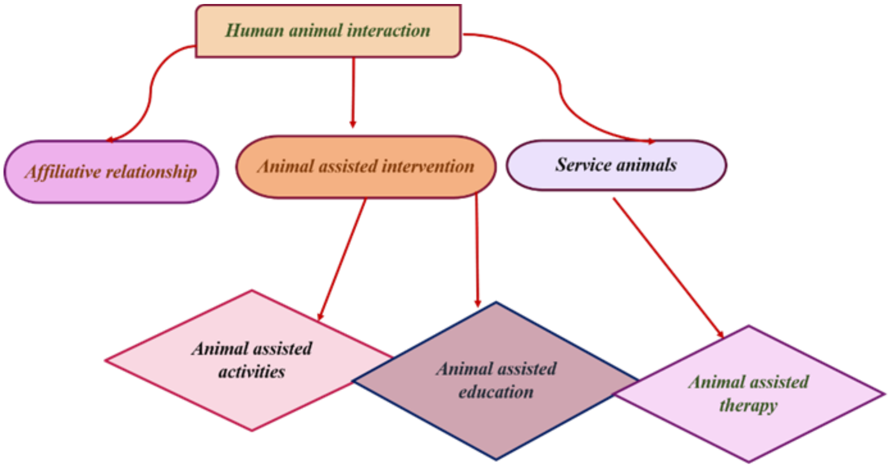

Fig. 2: Categories of animal human relationships

ambiguous and suggestive signals by rat tickling and contact with pigs. Positive human animal relationship development provides profits for long period. The persistence effect of positive human relations is five to sixteen weeks for pigs, six to eight months for dairy cattle, twenty-four months for beef cattle, twenty-five months for goat and six to eight months for horse makes it an intervention with lifelong effects. Hereafter, positive human animal relationship can provide positive welfare consequences, like better anxiety flexibility, social maintenance, ecological enrichment, positive affecting states and profits for human (Hausberger et al. 2002). The benefits of human animal relationship are briefly described below:

Social Benefits

When people involve in discussion or enter into social condition sometimes, they face anxiety and high blood pressure. Animals encourage our aptitude to link with others around us by boosting discussion and assisting in drop of uneasy approaches people may experience (Henry et al. 2005).

Behavioral Benefits

Animals introduce behavior and responsibility into survival of children as family. Animal is deliberated a child's child and it has been observed that 48% of relations reflect their pet as a family member (Sankey et al. 2010).

Emotional Effects

Animals are center of consideration as most of the animals, particularly pet and domesticated animals typically do things that make us laugh (Henry et al. 2006).

Physical Effects

Watching animals' physical activities and exercise, marks a better physical power in human beings. For example, common side effects of Alzheimer's disease are loss of appetite and weight. Patients of Alzheimer's sit in front of fish tanks in mealtime. While watching fish through normal intake periods, patients establish metabolic achievements in their weight and experienced a rise in appetite. This study shows the impact of human-animal relationship upon the ultimate health of human (Sankey et al. 2011). Relationship between human and animal is illustrated below in Fig. 3.

Disadvantages of Human Animal Relationship

There are many advantages of positive human animal relationships, however there are some disadvantageous of this relationship as well. For example, contact of animal can be problematic to handle because of fear of individuals, though animals are in fear with unfamiliar handlers and handling site that take lengthy to move and walk than those who have positive human relations which represent an interaction and awareness of location between human and animals. Safety and trust of followers is necessary as animals with slight fright can be risky, specifically in case of wrong human attitude that can be dangerous or possibly aversive events such as bite of animal that can occur due to its close interaction or management. Proper animal's management can diminish risks of violence and injuries. Positive human animal relationship may set limits such as safe space and avoid dangerous interactions. Group animals normally learn to separate suitable social activities from unsuitable during their improvement that is part of socialization, development and improvement of social services. Development of socialization may also affect animal's actions toward individuals (Mason 2004).

States of Human Animal Relationship

States of human animal relationship are contact, appreciation and development of sensitivity toward animals, learnings through observation, protection and defense or animal assisted activities (Sherman et al. 2008) as described in Fig. 4. Contact of animal represent animal behavior. Appreciation and development of sensitivity toward animals is important state of relationship in which sensitivity is perceived by animals like dogs detect if we fear and birds realize if anyone approach to them warily. Learnings observation requires acquisition of new behavior, adaptation and existing one. Learning by animals requires us to imitate their behavior or relate their aptitudes to human lifespan.

Protection and defense is fourth state and play therapeutic role that is achieved by contact of animals, development of sensitivity of animals and learning through observation.

Assisted activities related to animals is the best recognized state while human animal association is mentioned from an informative or therapeutic point (Tallet et al. 2009).

The Five Freedoms of Animals

Freedom of animal must be kept in mind. There are five states of freedom of animals that are as follows:

- ➢ The animal must be free from hunger, malnutrition and thirst and animal must easily be approach to water and suitable diet (Fig. 5).
- ➢ The animal must be free from thermal and physical discomfort and it must provide proper shelter & comfortable resting area.
- ➢ The animal must be free from pain, disease and injury.It must facilitate with suitable prevention by using vaccine and deworming and treat in case of any diseases after proper diagnosis.
- ➢ The animal must be in a state to express its normal behavioral as animal must need adequate space, proper services and company of further animals.
- ➢ The animal must be free from any fear and distress in order to prevent mental health suffering (Hausberger et al. 2007).

These five freedoms were established by the government of United Kingdom in a book named as "Animal Machines" written by Ruth Harrison in year 1964.

Consequence of Human Animal Relationship on Animal Productivity

Positive interaction can minimize human distress, like training may improve production of farm animals. According to a study human animal relationship may decrease resources that are required to animals to react connections of human and these can be consumed for productivity. In case of poultry, positive relationship improves the development in feed efficacy and weight gain in chickens. Though, positive interaction sometimes had insignificant or adverse effect on growing performance (Bourjade et al. 2009). Physical interaction involved pick up and patting of chickens seemed to be extra communicating than visual interaction in case of broiler hen. In case of laying chicken, regular visual interaction reduced upgraded egg production. Human fear may sometime be deliberated such as unfortunate growth and reproductive performance of different animals (Tallet et al. 2009). Gilts (female pigs under the age of 1 year) with pleasant treatment had improved weight gain and feed inefficiency than in the unpleasant management. Gilts in unfriendly atmosphere showed lesser pregnancy rate than those in friendly environment (Topal et al. 2003). Pigs raised up in huge clusters may take psychosomatic protection from colleagues in group. There may be few human interactions and productivity in farmhouse animals. Pleasant human interaction has insignificant effect on milk production and has less signs of anxiety in milking as compare to those cattle that are under stressed in new environment. It is summarized that human interaction is not satisfactory to diminish neuroendocrine response to isolate stress (Sherman et al. 2008).

Consequence of Human Animal Relationship on Animal Health

The immune system is an autonomous system and combined with other biological systems that is delicate to the brain.

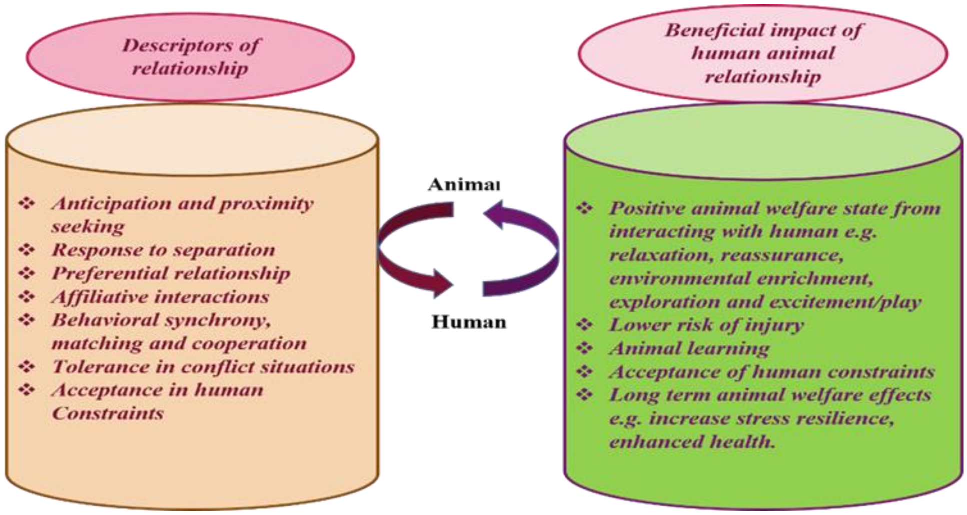
Descriptors of relationship
Anticipation and proximity seeking
Response to separation
Preferential relationship
Affiliative interactions
Behavioral synchrony, matching and cooperation
Tolerance in conflict situations
Acceptance in human Constraints
Animal
Human
Beneficial impact of human animal relationship
Positive animal welfare state from interacting with human e.g. relaxation, reassurance, environmental enrichment, exploration and excitement/play
Lower risk of injury
Animal learning
Acceptance of human constraints
Long term animal welfare effects e.g. increase stress resilience, enhanced health.

Fig. 3: Different dimension of positive human animal relationship for animals. Arrows represents interaction between animals and human

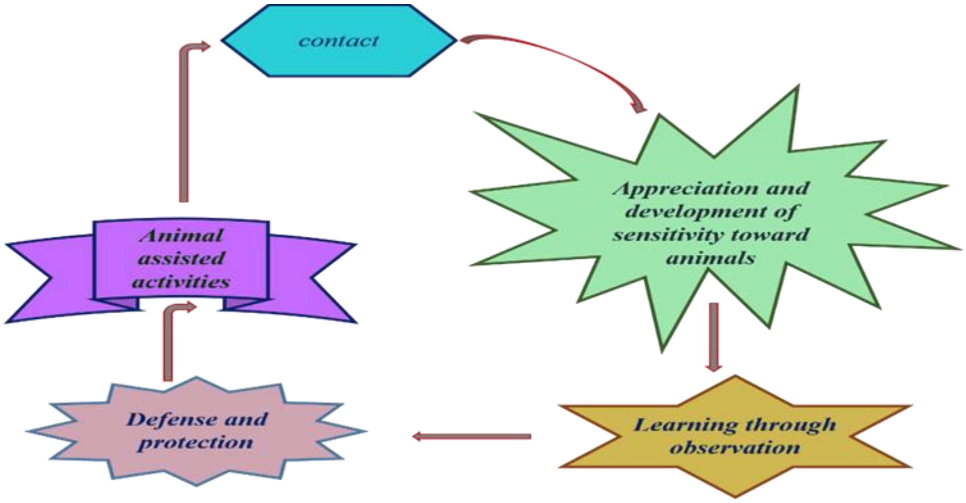
contact
Appreciation and development of sensitivity toward animals
Learning through observation
Defense and protection
Animal assisted activities

Fig. 4: States of the human-animal relationship

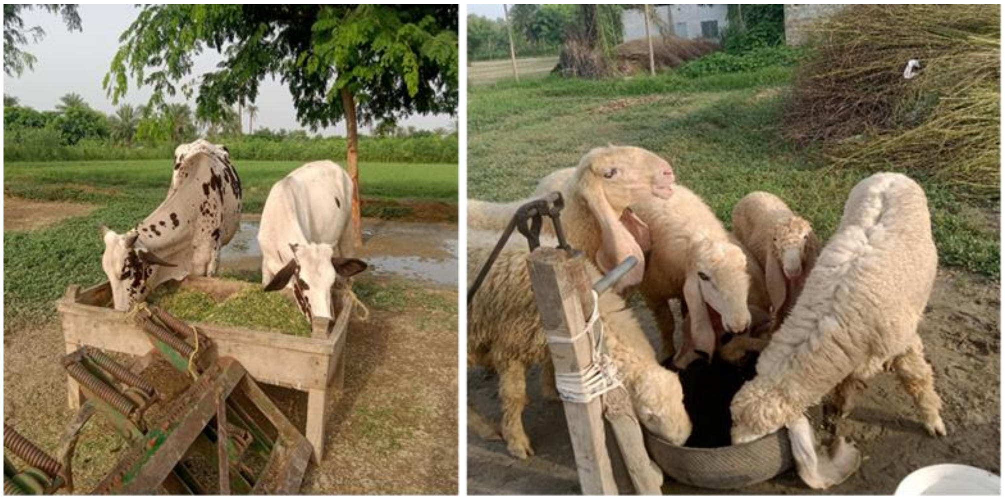

Fig. 5: Examples of animal welfare like proper feeding and watering

Human interaction alters the brain morphology and physiology. Farm animals sometime show certain degree of immunosuppression. Hypothalamic pituitary activation of adrenal axis and the sympathetic adrenal medullary axis leads to chronic catecholamines and corticosteroids production respectively. Granulocytes, lymphocytes, macrophages and monocytes exhibit corticosteroids receptors and catecholamines that can change cellular transferring,

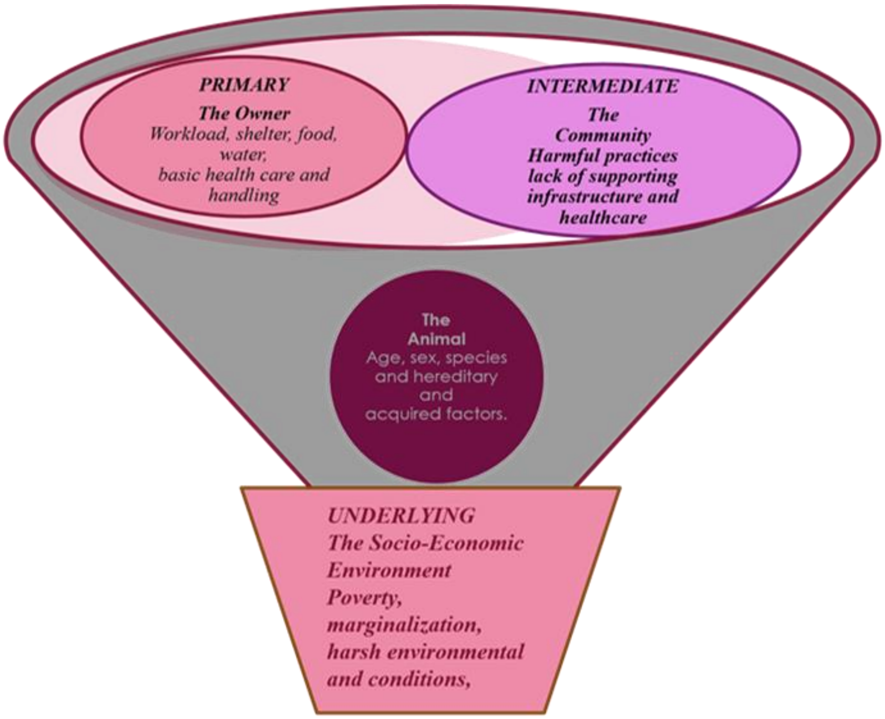
PRIMARY
The Owner
Workload, shelter, food, water, basic health care and handling
INTERMEDIATE
The Community
Harmful practices lack of supporting infrastructure and healthcare
The Animal
Age, sex, species and hereditary and acquired factors.
UNDERLYING
The Socio-Economic Environment
Poverty, marginalization, harsh environmental and conditions,

Fig. 6: Influence of Human interaction resource and environment on animal

secretion of cytokine, proliferation, cytolytic activity and antibody production. Positive human animal interaction in farm animals may boost animals' health (Parker et al. 2012). Visual interaction from zero to three and zero to six week of age may increase antibody production against Newcastle disease. Pleasant human interaction of hens can improve cell mediated immune response toward mitogen than those hens that received bad human interaction. The human interaction improves disease resilience and immune response that effect on physiological anxiety response (Purewal et al. 2017).

Influence of Human, Animal and Environment

Concept of animal welfare focuses on three main factors as mentioned in Fig. 6. First factor is the human attitudes and practices like traditions and the second factor is animal itself and resources that are available for example shelter must provide to animals, human to treat animal in case of any infection and information about prevention for example vaccination or deworming of animals. Third important factor is environment in which animal lives and surrounding area where animal need to work. Human, animals and environment are interconnected or have strong influence on each other (Schreiner 2016).

Domains of Animal Welfare

Animal welfare domains include behavior, nutrition, health and environment which emphasizes on physical difficulties. The behavior domain emphasizes on surroundings such as environment, humans and animals which bounds appearance of natural behavior or stance a dare an animal has to respond. All these factors fall into the domain of emotional states (Rodriguez et al. 2018).

Effects of Human Animal Relationships

Effects of human animal relationship are categorized in to behavioral, educational, physiological, and psychological categories (Fiocco et al. 2017).

Behavioral

Human animal relationship is a social behavior because of its social nature. Affiliative connections to child pet ownership that support positive relations, responsibility, autonomy and decline aggression (Purewal et al. 2017). The obvious objective to assist social relationships can be helpful in treatment for autism, intellectual disability and dementia. Working animals aid social dealings and established experience of more positive social relations when their service pup is present than deprived of (Muñoz Lasa et al. 2015).

Educational

Human animal interaction provides motivational, emotional and social profits to students in all education stages. Prime classrooms of education use dogs to encourage behaviors in order to develop performance and experience such as concentration, relaxation and motivation in classrooms through behavioral and reading programs. Furthermore, exam related tension, tension release periods, where scholars link up with animals for short time at their willpower and follow teaching space in campuses to spread large number of students (Busch et al. 2016).

Physiological

The physiological effects of human animal relationship related to stress, physiological activity and bonding. The physical profits can be direct, such as reduced blood pressure and indirect for example oxytocin hormone that elevate in bonding (Souter et al. 2007).

Less physical activity can be dangerous part of human fitness to induce diabetes, cardiac disease and several other diseases. The physical activity that dog's owner needs like dog walk is mutually advantageous and certify active lives for both holder as well as animal. Some animal related interferences that simplify physical activity, specifically for inactivated individuals. Walk improves nervous system damage, control limb and balance movement (Muñoz Lasa et al. 2015).

Bonding

Human animal relationship influences hormones that are associated with social activities. Oxytocin is hormone and a neurotransmitter that stimulates social bond and responds to relations in which both animals and humans are associated. Pet owners linked or look into eyes of dogs, which leads to an increased level of oxytocin in blood and urine of owner and dog (Coppola et al. 2006).

Psychological

Human animal relationship of different types produces positive psychosomatic effects in clinical and nonclinical people through lifetime. Pet holders are less lonesome, anxious and depressed. (Schreiner 2016). Human animal relationship not only improves over-all mood but can also decrease symptoms of emotive complaints such as anxiety, depression, behavioral illnesses, attention dearth, hyperactivity syndrome and some autism disorders (Busch et al. 2016).

Human animal Relationship Assessment

Animal welfare can be measured formally with the help of tools or informally with those findings that are built on knowledge. Both are very important and both should form by share of formal or informal involvement (De Meyer et al. 2020) Different ways are used to measure such relationship which are as follows:

Indicators

Biological alterations can occur after, before and during relations with humans. Indicators founded on structures of relations and reflect human animal relationship. Several indicators can differentiate different potentials of association and evaluate that animals have well affiliation than others however it is difficult to fix threshold where human animal relationship starts positively and indicators obviously reflect positive human animal relationship. The calculation of positive human animal relationship requires holistic investigation, given that numerous indicators must be measured together for understanding. Attention is mandatory in measurement of positive human animal relationship because the stimulus interrelate humans may be at time of contradictory with further stimuli (Normando et al. 2008).

Behavioral Changes

Behavioral changes are directly related with positive human animal relationship and their specificity toward it. Animal can show symbols of eagerness before the relations takes place, once human relations is expected and environment signal onset of human. These can be measured through appetitive symbols, like walking, communications and amplified behavioral transitions. For example, confined animal anticipate connection with humans, through enlarged surface observation and detection, these defensive behaviors associated with level of commitment in contact. These preventive signs can still be uncertain indicators as these can be representative of excitement in case of positivity & frustration in case of negativity depending on situation. The first response of an animal on entry of human at its location is an alignment reaction. Animal naturally turns consideration toward human, may be with many senses rest of visualization. The location reaction specifies that animal notices human presence, but is not obvious sign of relationship because its motivation reflects interest in case of positive and attention in case of negative state. On the other hand, body, head, ear movement and posture associated behaviors may aid to discriminate at least negative relationship and neutral to positive relationship such as cattle skull stays in normal position and ears not raised or even droopy while seeing to person and continuing rumination process (De Meyer et al. 2020). Once human enters animal's atmosphere attention seeking behavior is a sign of positive relationship. Approach is stimulus of situation and can be used with different signs. Though, a dearth of approach does not rule out positive relationship but may show low inspiration for physical communication at this phase and this accounts for conditions in atmosphere where many disturbances or challenges may follow such as feeding and relaxation. In several cases, latitudinal proximity is indicator of human animal relationship. Duration and number of relations started by animal is sometimes used as quality indicator of human animal relationship however measurable metrics do not inevitably reflect association because animal may moderate cooperation with human according to requirement. In this concern, advance research is necessary such as study complementarity, mutuality and behavior exchanges synchrony have been revealed in quality of parent child associations (Waiblinger et al. 2004).

Behavior synchrony is related to association in humans and locomotors synchrony is detected between dogs and pet holders. Moreover, dogs with poorer level of oxytocin receive further patting from their pet holder and represent dynamic interchange of human animal relationship. Behaviors and body position show approach and interaction with humans, reflect animal's commitment in communication and provide data about awareness and motivation of animal. Moreover, solicitation activities like touching, scratching and nudging with human hand and vocalizations are signs of animal's to engage and can interpret symbols of positive awareness of relationship. Animals may also show body areas where they desire to be patted such as ventral neck area in case of cattle, front area in case of pigs, or back in case of dogs (Bertenshaw et al. 2008). These behavioral responses expose susceptible body area that may be involved for level of trust which reflects positive human animal relationship, in furthermost cases, these behaviors reveal throughout intra-specific socio positive contacts, though there are various interspecies activities for example dog against wolf. Response of animal in human presence is clearly main symbol of positive relationship. Lack of anticipation reaction to humans is indication of animal's fear for human. Ears position changes such as frontward vs. lateral, reluctant and raised vs. flaccid are used to understand valence of human interaction like dog, horse, sheep and cow where as more delicate changes in facial appearance such as cat and parrot. Tail wiggling in dogs sometime mentioned as sign of amusement, it may be symbol of encouragement somewhat positive valence. In various species communications are sometimes linked with positive relations like buzz in cats. Rapid reduction in grief vocalizations and increased closeness looking for humans can understand as positive discernment of human presence such as goat and hand rear sheep. Dislodgment and delay behaviors in stretching dogs, licking of lip and muzzle observe in direction of upper limit may be negative signs that reflect unwillingness to interrelate or encounter motivations. (Muns et al. 2015).

Physiological Changes

Oxytocin is related to social procedures. Positive connections with humans increase oxytocin concentration. Positive human animal relationship and variations in concentrations of oxytocin is complex and cannot be easily understandable. Concentration of cortisol changes positive relations with direction that reflect keenness of dog and easing dog. Change in concentration of cortisol is time and circumstance dependent. Change in cardiac rate and its variability due to cortisol measures indication of autonomic reaction (Foster et al. 2012). For advance research physical changes required specifically neurotransmitter like opiods, dopamine and some immune parameters. Positive connections induce collection of immune and physiological changes in both humans and animals. Rabbits receive regular human interaction that shows lesser prevalence of atherosclerosis. Hens has advanced immune reaction, disease resilience and visual interaction with humans improved antibody reaction to Newcastle vaccination and reduced heterophil toward lymphocyte ratio and limitation in life (Baker 2004).

Neurobiological and Cognitive Effects

Mental preference has been widespread as secondary evaluation of situations through reviewing affect. Scratching of animals by human brings to positive judgment of uncertain hints, signifies that it persuades positive emotional condition. Positive human animal relationship leads to positive responsive conditions involves further study. Further methodologies depend on animal's memory Horses that are skilled use positive consolidation training with human communications that evoke human and spent more time. Ewe can also be taught to discriminate human looks and think of those faces for above two years and sheep also identify their caretaker deprived of pertaining. These verdicts support that positive human animal relationship can be long-term. Neurobiological studies of optimistic relationship are still in initial stage with use of practical ultraviolet spectroscopy, electroencephalography, and autopsy brain actions in dog, pigs, and sheep. Humanoid animal relationships can grow with fresh methods like neuroimaging in case of dog that permit noninvasive longitudinal neurobiological studies (Rault 2011).

Post interaction Changes

Maximum studies are based on biological deviations from the time of mankind existence. There are sum of variations that can reveal positive effect such as relaxation, post-consummatory and negative effect like separation distress, and searching performance. These interactions sometime ignored to deviations during communication. Directories contain ear hanging position in cattle, lower heart rate, break or well sleep in dog and better parasympathetic action in various species that elevate oxytocin concentration in brain. Signs of efforts to re-establish interaction, after disruption of contact, as showed by symbols of separation suffer or examine behavior as in dog and hand raised ewes. Symbol of human animal relationship are marks of pain, negative emotional conditions, incisive activities and sorrow when relation is interrupted. Advance research is necessary on optimistic human animal relationship that bring changes on animals. For illustration, temperate human contacts during benefitting or raising can clue to scarcer hostile connections between dairy animals once they return to flock and lesser adrenocortical action in calves (Mariti et al. 2018).

Why Should Animal Welfare be Measured?

Animal welfare should be measured due to following reasons:

- To monitor and evaluate impact of project running on animal's welfare.
- To match welfare position of animals between diverse locations or societies.
- To recognize welfare disputes, vary by dynamics such as season, work category, animal phase, sexual category or landlord practices. This material is then valuable to adapt program to specific cluster, period, mark animals with the poorest difficulties and public which is ready to involve with us.
- To ascertain welfare concerns which are happening within an animal population and community.
- To identify occurrence and harshness of different welfare problems i.e., what is going on to level of welfare in population
- To pick up if interconnection is making positive or negative modification.
- To allow targets to be produced at departure area, based on current welfare rank
- Re-assessment of animals can be directed at the end of a project or phase to provide animal's attentive constituent of project assessment.
- The animal centered data can be used to triangulate from further bases such as source, ecological and human based actions relevant to welfare (Wilson and Barker 2003).

Conclusion

Human animal interaction plays very important role in psychological health research, philosophy and practice mainly in family arrangements and social approaches. Animals provide many vital physiological, relational and psychological benefits. They influence by curing, animal support programs development, Community involvement and anticipation initiatives. Up till now, there is less study in field of animal mental health, healing value in health, human animal relationship, animal research and importance of this relationship in our current lives. Animals provide preference, recreation, deep affection, steadfast faithfulness, safety and reliability in our lives. These affections bring happiness, luxury to child and adults and also contribute to improve lives. Advance study is required to recognize how much variations in structures of relations reveal value of affiliation.

REFERENCES

Baker KC, 2004. Benefits of positive human interaction for socially housed chimpanzees. Animal Welfare 13: 239–245.

Bertenshaw C et al., 2008. The effect of different degrees of positive human animal interaction during rearing on the welfare and subsequent production of commercial dairy heifers. Applied Animal Behaviour Science 114: 65–75.

Bourjade M et al., 2009. Adult young ratio a major factor regulating social behaviour of young: a horse study. Plos One 4: 3- 6.

Busch C et al., 2016. Animal-Assisted Interventions for Children with Attention Deficit/Hyperactivity Disorder: A Theoretical Review and Consideration of Future Research Directions. Psychological Reports 118: 292-331.

Coppola CL et al., 2006. Human interaction and cortisol: can human contact reduce stress for shelter dogs? Physiology and Behavior 87: 537–41

De Meyer D et al., 2020. Short Communication: effect of positive handling of sows on litter performance and pre-weaning piglet mortality. Animal Behavior 14: 1733–9.

Fiocco AJ et al., 2017. The Buffer Effect of Therapy Dog Exposure on Stress Reactivity in Undergraduate Students. International Journal of Environmental Research and Public Health 14: 707.

Foster T et al., 2012. Characterizing cognitive aging of spatial and contextual memory in animal models. Frontiers in Aging Neuroscience 4: 12.

Fureix C et al., 2009. How horses *(Equus caballus*) see the world humans as significant "objects". Animal Cognition 12: 643-654.

Hausberger M et al., 2002. A brief note on some possible factors involved in the reactions of horses to humans. Applied Animal Behaviour Science 76: 339-344.

Hausberger M et al., 2007. Lower learning abilities in stereotypic horses. Applied Animal Behaviour Science 107: 299-306.

Hausberger M et al., 2008. a review of the human horse relationship. Applied Animal Behaviour Science 109: 1-24.

Henry S et al., 2006. Influence of various early human-foal interferences on subsequent human foal relationship. Developmental Psychobiology 48: 712-718.

Henry S et al., 2005. Human mare relationships and behaviour of foals toward humans. Applied Animal Behaviour Science 93: 341-362.

Hunt SJ et al., 1992. Role of small animals in social interactions between strangers. The Journal of Social Psychology 132: 245-256.

Mariti C et al., 2018. Effects of petting before a brief separation from the owner on dog behavior and physiology: a pilot study. Journal of Veterinary Behavior 27: 41–46.

Mason GJ, 2004. Can't stop, won't stop: is stereotypy a reliable animal welfare indicator? Animal Welfare 13: 57-69.

Muñoz Lasa S et al., 2015. Animal assisted interventions in neurorehabilitation: a review of the most recent literature. Neurología 30: 1-7.

Muns R et al., 2015. Positive human contact on the first day of life alters the piglet's behavioural response to humans and husbandry practices. Physiology and Behavior 151: 162–167.

Normando S et al., 2008. Effects of an Enhanced Human Interaction Program on shelter dogs' behaviour analysed using a novel nonparametric test. Applied Animal Behaviour Science 116: 211–219.

Parker R et al., 2012. Assessment of quality of life in equine patients. Equine Veterinary Journal 44: 244–249.

Purewal R et al., 2017. Companion Animals and Child/Adolescent Development: A Systematic Review of the Evidence. International Journal of Environmental Research and Public Health 14: 234.

Rault JL, 2011. Separation distress in artificially reared lambs depends on human presence and the number of conspecifics. Applied Animal Behaviour Science 132: 42–50.

Rodriguez KE et al., 2018. The State of Assessment in Human-Animal Interaction Research. Human-Animal Interaction Bulletin 6: 63-81.

Rybarczyk P et al., 2001. Can cows discriminate people by their faces? Applied Animal Behaviour Science 74: 175-189.

Sankey C et al., 2010. Positive interactions lead to lasting positive memories in horses, *Equus caballus*. Animal Behavior 79: 869-875.

Sankey C et al., 2010. Reinforcement as a mediator of the perception of humans by horses *(Equus caballus)*. Animal Cognition 13: 753-764.

Sankey C et al., 2011. Asymmetry of behavioral responses to a human approach in young naive *vs.* trained horses. Physiology and Behavior 104: 464-468.

Schreiner PJ, 2016. Emerging Cardiovascular Risk Research: Impact of Pets on Cardiovascular Risk Prevention. Current Cardiovascular Risk Reports 1: 02.

Sherman BL et al., 2008. Canine anxieties and phobias: an update on separation anxiety and noise aversions. Veterinary Clinics of North America: Small Animal Practice 38: 1081.

Souter MA et al., 2007. Do Animal Assisted Activities Effectively Treat Depression? A Meta-Analysis. Anthrozoös 20: 167-180.

Tallet C et al., 2009. How does the method used to feed lambs modulate their affinity to their human caregiver? Applied Animal Behaviour Science 119: 56-65.

Terlouw EMC et al., 2005. Repeated handling of pigs during rearing. Refusal of contact by the handler and reactivity to familiar and unfamiliar humans. Journal of Animal Science 83: 1653-1663.

Topal J et al., 2003. Attachment behavior in dogs *(Canis familiaris)*: a new application of Ainsworth's strange situation test. Journal of Comparative Psychology 112: 219-229.

Waiblinger S et al., 2004. Previous handling and gentle interactions affect behaviour and heart rate of dairy cows during a veterinary procedure. Applied Animal Behaviour Science 85: 31–42.

Waiblinger S et al., 2006. Assessing the human-animal relationship in farm species: a critical review. Applied Animal Behaviour Science 101: 185-242.

Wilson C and Barker SA, 2003. Challenges in designing human-animal interaction research. American Behavioral Scientist 47: 16–28.

8

Global Warming: A Neglected Conundrum from One Health Perspective

AUTHORS DETAIL

Muhammad Umair Waqas[*1], Ifra Chaudhary[1], Kashif Hussain[1], Asghar Abbas[1], Atif Rehman[*1], Baseer Ahmad[1], Muhammad Asif Raza[1], Junaid Ali Khan[1], Ali Haider[1], Ahsan Anjum[1], Waqar Zaib[1] and Hafeez ur Rehman Ali Khera[1]

[1]Faculty of Veterinary and Animal Sciences, MNS-University of Agriculture, Multan, Pakistan
*Corresponding author: umair.waqas@mnsuam.edu.pk: atif.rehman@mnsuam.edu.pk

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INTRODUCTION

The elevation in the average temperature of our planet has altered the food chain, ecosystem, weather, species balance and environment of the earth over a stretch period of time is termed as a Global Warming, which is a phenomenon well established and documented in the existing literature (Venios et al. 2020). This constant increase in the temperature results in the carbon emission, present in our atmosphere, at a much higher rate and hence burdening the greenhouse effect. In a last century or so, our planet, has witnessed the average increase in a temperature by at least 1.0 degree Fahrenheit (two-fold as quick as any other time span in the previous 10 Centuries) (Aptroot and Van Herk 2007). The melting of glaciers, the thawing of Arctic permafrost, the deforestation of earth, the thinning of icecaps and the pollution of our air has created a panic in general and causing horrific consequences such as floods, earthquakes, demolishing of food systems, disturbing food chains and health disasters (Butler 2018). There is more and more evidence that this increase in the average temperature of earth is responsible for the increase prevalence and cumulative incidence of many diseases of animals and human origin. It is also well established that human life style such as our interaction with our environment is a major reason behind the increased greenhouse effect (Miles-Novelo and Anderson 2019). The recent data has revealed that anthropogenic activates such as waste management activities, abuse of fossil energy, intensive farming, more consumption, rapid mining, extensive industrialization and deforestation are the prime reasons for the release of toxic gases, such as carbon dioxide, methane, nitrogen oxide and other lethal gases, which are causing the global warming through the greenhouse effect (Kim et al. 2014). This phenomenon has also seen as a concern from one health perspective. One health is a recent concept that emphasis on a fact that environment, humans and animals linked with each other and certain risk factors affect all three components of one health in one way or the other. Therefore, it is very important to look into all three components from same lenses and address the risk-factors from the perspective of humans, animals and environment (Butler 2018).

A Triad of Concern: Climate Alterations, Health Crises and Vulnerability of Our Civilization

Anthropogenic global warming is an established risk factor for human and animal health when teamed with social, economic, communal and other environmental factors (Butler 2018). In 1988, a testimony was presented to the US Congressional committee by the prime climate scientist, James Hansen with the other three top ranking researchers of National Aeronautics and Space Administration, which stated that “it is 99 percent sure that the increasing amount of carbon dioxide and various greenhouse gases in the atmosphere are the leading cause of global warming as these gases increase the Earth’s temperature” (Butler 2018). This revelation was given a space on front page of world’s leading newspapers such as New York times. The 1989 editorial of New York Times stated that “climate change, UV radiations of certain frequency, and thicken tropospheric ozone will significantly affect the global food chain and food supply, and potentially damage our food systems by impairing the agriculture” (Issar et al. 2004). This will increase the prevalence of mal-nutrition globally. Environmental related health risks not only combine with communal and social variables but also with other "purely" pre-disposing factors (Bryson 1988). For example, temperature rise has a direct impact of heat on human well-being, age, gender, underlying diseases, humidity, physical activity, life style, hydration, and also by work, economic status and vulnerability. For example, the impact of heat on brick-worker in Pakistan is different than its impact on an athlete. Other elements that influence the impact of heat include the quality of housing, the availability and access to good and affordable air conditioning, and energy subsidies, if available (Kalkstein et al. 1993). Moreover, these aspects are also determined by socioeconomic status and stability of local governments. Climate change has more drastic and direct effects on the socioeconomic aspects, for instance, starvation, conflict crisis and mass displacement, is witnessed in the climate

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effected regions. Diligent efforts are being made to determine the health consequences, related to climate change, such as heat's impact on health and spread of infectious diseases in vulnerable populations (Macklin and Lewin 2015).

There is high probability that if civilization collapses, the dividend would be hunger, violence, lawlessness, population dislocation, diseases outbreak and environmental hazards. It is more likely for a heat wave to crumble the world economy through its detrimental consequences (Rich 2018). The internal displacement in Syria is a most recent example of succession of heat waves, which began in 2011 and resulted in hunger and failure of food systems. The fear looms that such catastrophic events have power to shatter the health systems, along with ever increasing nutritional related disorders (Butler 2008). This will not only increase the incidence of life style diseases but also infectious disorders due to compromised immune system (Hansen et al. 2007). The alarming increase in the infectious diseases, might lead to integrative cascade of failures, which could result in a worldwide civilization disintegration (Kemp et al. 2022).

Globalization and its Effects on Climate Change and Human Health

The globalization of world is a result of economic, social, religious and industrial revolution in last two decades. However, the globalization, as evident from recent examples, is a social determinant for certain diseases (Kim et al. 2014). Therefore, more efforts have been made to rectify the problem through public health initiatives, remodeling of health care systems and sharing of health data (McMichael et al. 2006). The global development is an unquestionable determinant of people's health, public health initiatives and regional health care systems (Patz et al. 2005). Anthropocene, the present geologic period is in acknowledgement of Homo sapiens' worldwide power, disrupting the Earth's natural structures, way past the limit, which is known to be safe for the sustenance and survival of species on this planet (McMichael et al. 2006). The significantly raising global circulation of toxic organic chemicals, the extinction of species at an alarming rate, and uncontrollably exceeding human caused climate changes (Haines et al. 2006). These changes are not only detrimental for our environment but also lethal for human and animal health. Human-leading global warming has serious implication on our food production and value chain, causing the severe problems of malnutrition among the vulnerable population, more outbreaks of infectious and non-infectious diseases, epidemics of skin allergies and shattering of health- systems. The sharing of knowledge, more sustainable food systems, holistic policy and coordination among different sectors are important elements to counter the outcomes of global warming and climate change for the achievement of health goals (Luber and Prudent 2009).

Climate change imposes a complex threat, which in anthorpocene syndrome of human and global warming, is one of its detrimental aspects for depletion of ozone layer, land degradation, decreasing soil fertility, ocean acidification, biodiversity endangerment, depleting fresh-water resources, disruption of global nitrogen and phosphorus cycles and ecosystem malfunctioning. Human caused global warming by a constant increase of 0.7°C since 1950 (McMichael 2013). In a last ten years, there is an alarming increase in an annual worldwide CO2 emission, a rise in the sea level, arctic glacier loss, and an increase in the severity of weathers. Severe changes in the rainfall patterns are to be observed with unexpected variable rainfall in different regions (Kim et al. 2014). Fig. 1 depicts the globalization and alternative processes taking place in the three prime domains i.e., finance, sociology and ecology. Their basic components, two-way interactions, and the key reality that all three domains impact the circumstances for and levels of population health are depicted.

Global money and labor movements, over-population, change in population dynamics, mortality and morbidity, economic growth and diversity, all have significant environmental impact. Especially the rapid accumulation of greenhouse gases is the fundamental reason of contemporary climate changes. These prime environmental alterations have a variable and far-reaching consequences for human well-being (Kim et al. 2014).

The climate change, social variables and environmental expressions have serious implications on human health behavior. The climatic changes that directly influence the natural ecosystems and cultural dynamics such as farming, food crops, water resources and the patterns of communicable diseases, are more likely to produce health hazards in the population (McMichael 2013).

Initial and earlier phase of climate change have some health benefits. Milder winters in variable zones will result in shortened winters mortality by stroke and cardiac arrest. Whereas hot winds with lesser humidity in other less elevated locations may lower vectors prevalence which may result in lower incidences of neglected tropical diseases (McMichael 2013). The people from different socio-economic status are going to be affected in different ways by climate change. Low –income people are more vulnerable to nutrition related disorders such as undernutrition, diarrhea, communicable diseases and migrations-related-disorders, whereas affluent people are more likely to be affected by life style diseases such as CVDs, Obesity, Hypertension, Mental disorders and drugs related ailments (Haines et al. 2006).

The control of health hazards pose by these global effects through primary prevention is a tough job at hand. The concept is beyond the traditional understanding of prevention, causality and democratic resources but needs the conceptual insight of the phenomena. Undoubtedly, newer and better techniques are needed to damp the present and imminent health hazards that are related to climate change. Powerful collaboration and alliances must form between health sector and other relevant sectors to reconstruct the human society plans, transport, create, utilize, disseminate, and produce more electricity to ensure that people live in a healthy, secure, productive and sustainable manner (Gomez et al. 2020).

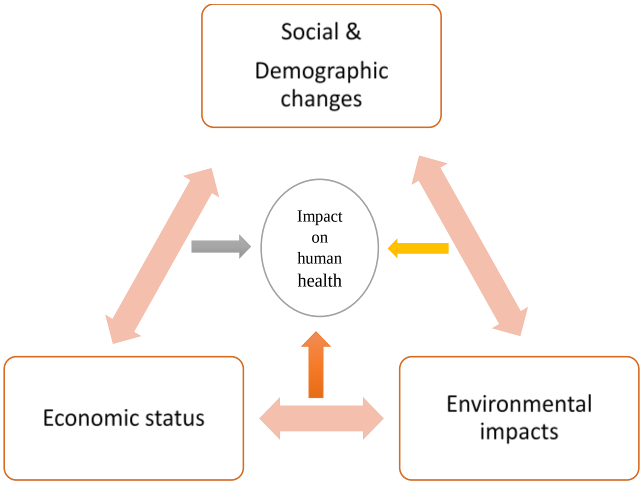

Fig. 1: Influence of Globalization on Human Health

Food Safety and Climate Crises

Food production and safety is largely concerned with the climate changes as it disrupts the food chain from its initial phase (primary production) to its last phase (consumption) (Haines et al. 2006). Climate change has an established effect on food production, safety, value chain sustainability and public health. Climate change dependent natural phenomenon's such as temperature, intense weather, patterns of precipitation, ocean warming and acidification and air pollution pathways, determine the safety of food chain (Tirado et al. 2010). Frequent variations in climate might influence the social and economic factors of food systems such as agriculture, diversification. Changing climate might influence the social and economic factors of food networks like agriculture, forms diversification, livestock raising, feed formulation and trade (Herrera et al. 2016). Calamities such as floods, hunger, poverty, and droughts can cause pollution and contamination of irrigated and drinking water, soil, animal feed, air and land with various infectious, carcinogenic and toxic chemicals, especially in the drains, industrial and farming sites. Hence, it is primarily important to maintain the cleanliness of land and water reservoirs after any natural disaster (Van der Spiegel et al. 2012).

Climate changes alters the conventional ways of farming as well as threatens the food security which ultimately influences the human diet and nutrition patterns. Approach to diversified, high-quality diets may become burdensome as climate change negatively influences the entire process of food production and food marketing (Tirado et al. 2010). Under production, over consumption and wastage resulted in reduction of nutrient rich food products and ultimately result in under-nutrition and compromised immune system, especially in developing world. Even in "business as usual" scenarios the health and nutrition related consequences are expected to deteriorate further (United Nations System Standing Committee on Nutrition Secretariat 2010).

The underlying determinants of food safety like farming methods, crop cultivation techniques, maintenance of plant health, food trade, animal food production, processing, transport, handling and consumption of food are all down-graded by the climate change (Kerr and Wilson 2018). These put a lot of risk for human and animal health along with socio-economic factors. A comprehension of these threats and realization of unpredictability of the climate change consequences is a primary initiative to combat the new food hazards (Brown et al. 2015).

Human health is directly influenced by the climate change via the down-grading of food safety by means of shifting temperature, rainfall, and humidity, and natural catastrophes like floods, drought, tsunamis and storms. These climatic elements have an impact on the health of plants and animals, and also determines the quality and quantity of food production and are potential causes of foodborne infections (Fraser 2006). Malfunctioning and deterioration of ecosystem, like the increasing land, air and water pollution, soil and mineral down-gradation have ramifications for production of foods and its nutritional status. The safety of human health lies within the important links and feedback processes that are critical through the food chain, environment, and community (Brown et al. 2017).

Deterioration of climate can increase poor nutritional status in multiple ways; threatening the food security (access, availability and affordability of food), child feeding, child care practices and reliable health care services. Climate change influences the quality, availability and pricing of food, which in return influence the total caloric intake and intake of nutrition dense food. Lack of micronutrients and stunting may, therefore, be impacted by this (Fanzo et al. 2018).

The whole food supply chain is encompassed by food system, that begins through the farming and agricultural production of food and ends with the proper harvesting, processing, handling, storage, transport and costumer consumption of the food. It is anticipated that the effects of socioeconomic variables on climate change would have a significant and diverse geographical and temporal influence on food systems (Vermeulen et al. 2012). According to socioeconomic considerations, the effects of global warming on agricultural systems are anticipated to be broad and diverse, both locally and through time. The food supply chain is a critical instrument for investigating the impact of climate crises on our food environment and assessing whether or not it may jeopardize nutritional results. As each link in the supply chain is analyzed for flaws and solutions to these vulnerabilities are developed, undernutrition and food insecurity can be addressed and "leveraged for change". The networks that control the food supply, determine the food availability and nutritional value. Other factors, such as personal preference and convenience, influence the meals people buy and consume. To evaluate a person's level of wellbeing and nutrition, a range of foods must be consumed. Diversity in diet is associated with adequate nutrition, particularly micronutrient sufficiency, as measured by the quantity of well-known fruits and vegetables, the amount of food derived from animal sources (ASF), and the variety of foods consumed (Wheeler and Braun 2013).

Each component of food chain is affected by climate change. Usually these effects are detrimental, but sometimes they can be beneficial, resulting in an improved and enhanced production and higher crop yield. However, these beneficial impacts are overshadowed by the negative effects (Ericksen 2008). Climate change intensifies humidity in wet lands and dryness in dry lands, in terms of food production. This would worsen the water and heat situation in already underline areas, pests in crops and illness in livestock. In the mid to high latitude regions such as east Africa and Andes the reduced cold limitations might prolong the growing seasons, but in the southern regions of the of the globe an increased heat and water stress might be witnessed, which would reduce the crop yields and a shift towards the better productions regions is expected (Fanzo et al. 2018).

There is a fundamental relationship between food safety and climate change, since climate change affects the agricultural production and may cause the issues of food security. For example, increase temperature results in the decrease yield of many crops and may result in the high price and difficulty in meeting the demand (Ericksen 2008). 19-29% of worldwide anthropogenic emission of greenhouse gases are produced by food system (Kerr and Wilson 2018). Out of which 80-86% of these greenhouse gases are produced by the agriculture production, which also includes the emission from the land covered changes (Kerr and Wilson 2018). The environmental impact of livestock farming is complex concept. Ruminants, more specifically like beef and cattle are more impacted by the climatic changes rather than the other species like chicken and pigs, due to their higher feeding efficiency (Parry et al. 1999).

The food system is being impacted by climate change and unpredictability at every stage, from cultivation to manufacturing and distribution to consumption. Shellfish, meat, dairy and organic products are specifically vulnerable. The health repercussions include decreasing nutritional status due to pricing fluctuations and gap in demand-supply chain and more incidence of foodborne ailments. Climate-smart agriculture is a useful tactic for addressing climate change issues, but more work needs to be done to connect these methods to nutrition and diets, particularly for the most prone communities. In addition, agriculture practices need to be gender and environment-sensitive. The corporate sector, charitable organizations, and governments must collaborate to improve nutrition as it relates to climate change (Brown et al. 2017).

Climate Crises and Animal Health

Climate change is one of the most potent risk factors that affects the health of animals and humans. Different environmental variables such as relative humidity, environmental pollution, extreme temperatures and unexpected atmospheric changes have either direct or indirect relationship with onset of diseases in animals (Van and Coetzer 2008). Such uncalled environmental changes are leading to heat stresses in animals. The duration of heat stress leads to negative consequences which animals may experience such as metabolic alterations, immunological suppression, oxidative damage and death (Fig. 2) (Lacetera 2019).

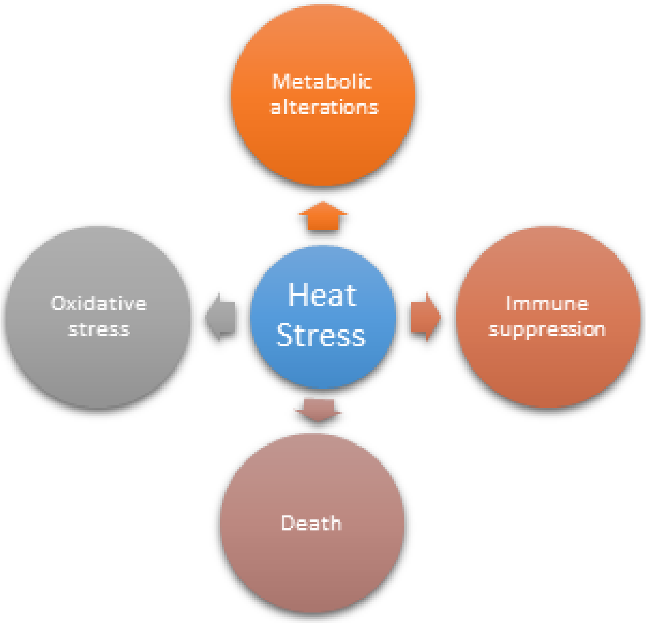

Fig. 2: Consequences of heat stress

Numerous clinical problems in farm animals, including those that are crucial for animal production and human health, may be caused by oxidative stress. The imbalance of oxidant and antioxidant molecules that results in oxidative stress can be brought on by an overabundance of oxidative chemicals or a deficiency in antioxidant chemicals (Forman et al. 2008).

The immune system was first developed as a set of mechanisms to protect the host from the incursion of dangerous organisms. There are several variables that can affect how well the immune system is able to work. According to a number of studies, heat stress can negatively affect an animal's immune system's performance (Skuce et al. 2013). Depending on the species, genome, breed, social status, age, degree of acclimatization, and length of exposure to unfavorable conditions, heat stress impacts immune function in a number of ways (Kerr and Wilson 2018).

Extreme weather conditions are responsible for high mortality rate due to heat fatigue, heat syncope, heat stroke, heat cramps and organ dysfunction (Pinto et al. 2008). The increase in body temperature by 3 to 4 degrees Celsius over normal lead to the increase in heat related problems. The danger of fatality persisted for the 3 days that followed the end of heat wave. The number of fatalities increased as the heat wave lasted longer. The good predictor for climate affecting farm animals is "temperature-humidity index" (Mas-Coma et al. 2008). According to an epidemiological study done on dairy cows, the daily minimum and maximum humidity temperature measurements are 70 and 80, respectively, above which the risk of heat-related deaths enhanced (Nardone et al. 2010).

There are numerous stressors (fishing habitat loss, pressure, disturbance, pollution, and invasive species) affecting the fish population are made worse by the climate change. The impact of other human activities, which are usually greater and more immediate, must be taken into consideration when evaluating climate change (Slenning 2010). Examples of these processes include changes in orbital deviation and solar radiation of the earth mountain-building and continental drift, and variations in concentrations of greenhouse gases. Many elements of climate, including the icecaps and oceans, take a long time to adapt to atmospheric change due to their enormous size. This climate-system may thus take millennia to properly adapt to recent exogenous changes. Numerous studies made the assumption that baseline biophysical processes, adaptability, and socioeconomic situations will change. According to various studies, there will be increasing detrimental effects after the global mean temperature rises by 3 to 4°C (Babinszky et al. 2011).

In addition to altering fisheries and aquaculture, greenhouse gases especially carbon dioxide in the environment are also affecting sea surface, wind pattern, sea level, air temperature, intensity of tropical cyclones, rainfall, and oceans acidity (Sundstrom et al. 2014). These changes are also affecting the earth's climate, freshwater ecosystems coasts and oceans. As a result of these changes, the life, productivity and the distribution of freshwater and marine species are shifting and altering the biological processes, hence, affecting food-web (Black et al. 2008). We don't yet know how these changes will affect the people who depend on fisheries, aquaculture, and aquatic ecosystems. Rising ocean temperatures and acidity point to a continuously declining ability of the oceans to store carbon, raising concerns on a global scale that were expressed in the Monaco protocol (Zinsstag et al. 2018).

The most alarming of these human consequences is the rise in carbon dioxide levels brought on by emissions from burning fossil fuels, aerosols and cement production. Concerning additional aspects are their involvement in altering climate, and measures of climatic variables, both independently and in combination with other causes. These factors include ozone depletion, land use, deforestation and animal agriculture (Zinsstag et al. 2018).

In order to calculate a long-term average, tidal gauge readings have been used to estimate the worldwide sea level change for a large portion of the past century. Aquatic ecosystems are being radically changed by rising ocean temperatures and acidity (Khoshnevis and Shakouri 2010). Fish production and distribution in freshwater and marine environments are changing as a result of climate change. Therefore, the carbon storage and capturing ability of the seas are being affected. This poses a potential life threat to the marine species (Cochrane et al. 2009). Changes in water usage and rainfall patterns have an impact on inland (freshwater) aquaculture, while the consequences of sea level rise put coastal fishing communities on the border-line of climate change (De Silva and Soto 2009). Despite the fact that fisheries and aquaculture depend on healthy aquatic ecosystems and are significant contributions to food security and livelihoods, these facts are routinely disregarded and undervalued (Reid et al. 2019).

For 3 billion people, fish provides essential nutrition, and for four hundred million people in the world's poorest nations, at least half of their protein and minerals comes from meat. Fisheries and aquaculture provide a living for more than 500 million people in under-developed countries, either directly or indirectly (Reid et al. 2019). With an annual growth rate of 7%, aquaculture is the technique of food production that is developing at the quickest pace worldwide (Barange et al. 2018). With more than 37% of worldwide production, marine value-added products are among the most globally traded foods. The process of calcification, which marine species like shrimp, oysters, and corals use to form their shells, becomes more challenging for them as the water's acidity rises (Callaway et al. 2012). Many important species including zooplankton, which acts as a prime foundation for a marine based food system, have calcium cells and being affected by increased acidity in water. As a result, the whole aqua food web is being affected by "openings in the food system"(Doubleday et al. 2013).

Climate Crises and Ticks Transmitted Diseases

Ticks spread a wide variety of viral, protozoan and bacterial illnesses across many temperate and tropical regions globally (Medlock and Leach 2015). Blacklegged ticks are a particular problem in North America because they spread the bacterium *Borrelia* (*B.*) *burgdorferi* which is responsible for Lyme disease in southern and eastern parts of Canada. The increased number, types, activity level, and geographic spread of ticks in North America and evident migration of blacklegged tick are now the well documented effects of climate change. As a consequence, high prevalence of Lyme disease is recorded in Canada (Caminade et al. 2019).

Many climate and environmental factors are responsible for increased risk of tick-borne diseases. (Ogden 2017). The shifting in weather patterns, extreme temperatures, humidify, globalizations and other climate related factors are risk factors associated with increase cases of tick-borne ailments. People are also likely to alter their behavior in response to environmental changes, resulting in ticks coming into contact with both human and animal hosts for a longer period of time (Bouchard et al. 2019).

Each species of ticks has preferred environmental conditions and optimal biomes that may affect their global distribution and as a result may cause havoc among vulnerable population. For ticks to survive and successfully establish new tick populations, microhabitat elements like the composition of the soil are essential (Gray et al. 2009). The morphology of ticks, their animal/human hosts, and human exposure to ticks are all impacted by changes in habitat characteristics such as loss of

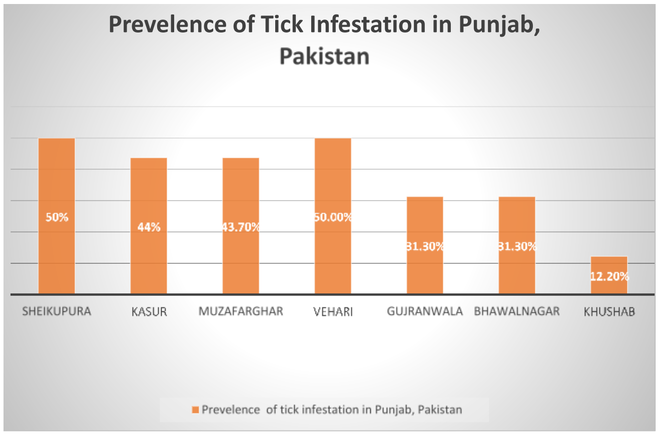

Fig. 3: Prevalence of various tick populations in Punjab, Pakistan

biodiversity, habitat fragmentation, land use and resource availability. For instance, agricultural reforestation led to an increase in deer populations, and ultimately more growth of *Ixodes* (*I.*) *scapularis* tick populations carrying *B. burgdorferi* (Caminade et al. 2019). Fig. 3 represent the prevalence of various tick populations in Punjab, Pakistan (Hussain et al. 2021),

The Climate Change and Potential Response of Public Health: An Integrated Policy

Despite the fact that public health is devoted to evidence-based practice, nothing is known about how to apply a scientific preparation approach to global warming awareness. Climate change has developed over the past 20 years from a possible problem to what now appears to be an actual threat to public health. When the potential impacts of weather change on health were first raised in medical literature, they were only considered as a possibility. Public health professionals today see climate change as a serious health issue, that will have long-term effects on people's health both locally and globally (Fox et al. 2019).

Public health and other sectors have shifted their attention to climate change adaptation (CCA) as climate change has gotten more extreme in recent years. Simultaneously, some have expressed concern about a lack of evidence to govern CCA projects. There has been little discussion of how evidence-based public health (EBPH) ideas may be applied to CCA activities and this problem originated from a desire to practice evidence-based medicine (Campbell-Lendrum et al. 2007).

Conclusion

It is very important to integrate the public health and climate change policy. The one health perspective of climate change is a serious concern and immediate efforts are required to address the issue. From Climate policy perspective, we need to advocate the concept of environmental health, agricultural reforms, news rules and regulations, ensuring the survival of ecosystem and sustainability of wood-web. The Public health policy must advocate the behavioral modification to minimize the environmental damage by human activities. Moreover, awareness programs are very critical from the health perspective. We need to see the climate change as a threat to entire universe and multi-sectorial holistic approach is only feasible solution to counter this calamity. We should not capitulate to this climate change disaster but need to solve the conundrum through a systematic approach where health policy should be integrated with climate policy to yield the hopeful results.

REFERENCES

Aptroot A and Van Herk CM, 2007. Further evidence of the effects of global warming on lichens, particularly those with Trentepohlia phycobionts. Environmental Pollution 146: 293-298.

Babinszky L et al., 2011. Impacts of climate change on animal production and quality of animal food products. In: Blanco J, editor. Climate change socioeconomic effects. Rijeka: InTech; pp: 165-190.

Barange M et al., 2018. Impacts of climate change on fisheries and aquaculture: synthesis of currrent knowledge, adaptation and mitigation options. FAO.

Black PF et al., 2008. Managing animal disease risk in Australia: the impact of climate change. Revue Scientifique et Technique 27: 563-580.

Bouchard C et al., 2019. Climate change and infectious diseases: the challenges: N increased risk of tick-borne diseases with climate and environmental changes. Canada Communicable Disease Report 45: 81-89.

Brown M et al., 2015. Climate change, global food security and the US food system. No. 105772.

Brown ME et al., 2017. Do markets and trade help or hurt the global food system adapt to climate change? Food policy 68: 154-159.

Bryson RA, 1988. Civilization and rapid climatic change. Environmental Conservation 15: 7-15.

Butler C, 2008. Sustainable health for all by the year 2100? International Journal of Public Health 53: 223-225.

Butler CD, 2018. Climate change, health and existential risks to civilization: A comprehensive review (1989–2013). International Journal of Environmental Research and Public Health 15: 2266-2276.

Callaway R et al., 2012. Review of climate change impacts on marine aquaculture in the UK and Ireland. Aquatic Conservation: Marine and Freshwater Ecosystems 22: 389-421.

Caminade C et al., 2019. Impact of recent and future climate change on vector-borne diseases. Annals of the New York Academy of Sciences 1436: 157-173.

Campbell-Lendrum D et al., 2007. Global climate change: implications for international public health policy. Bulletin of the World Health Organization 85: 235-237.

Cochrane K et al., 2009. Climate change implications for fisheries and aquaculture. FAO Fisheries and Aquaculture Technical Paper 530: 201-212.

De Silva SS and Soto D, 2009. Climate change and aquaculture: potential impacts, adaptation and mitigation. Climate change implications for fisheries and aquaculture: overview of current scientific knowledge. FAO Fisheries and Aquaculture Technical Paper 530: 151-212.

Doubleday ZA et al., 2013. Assessing the risk of climate change to aquaculture: a case study from south-east Australia. Aquaculture Environment Interactions 3: 163-175.

Ericksen PJ, 2008. What is the vulnerability of a food system to global environmental change? Ecology and Society 13: 2-14.

Fanzo J et al., 2018. The effect of climate change across food systems: Implications for nutrition outcomes. Global Food Security 18: 12-19.

Forman S et al., 2008. Climate change impacts and risks for animal health in Asia. Revue Scientifique et Technique 27: 581-597.

Fox M et al., 2019. Integrating public health into climate change policy and planning: state of practice update. International journal of environmental research and public health 16: Article # 3232.

Fraser ED, 2006. Food system vulnerability: Using past famines to help understand how food systems may adapt to climate change. Ecological Complexity 3: 328-335.

Gomez A et al., 2020. "Mitigation of emerging implications of climate change on food production systems." Food Research International 134: 109256.

Gray JS et al., 2009. Effects of climate change on ticks and tick-borne diseases in Europe. Interdisciplinary perspectives on infectious diseases 2009: Article # 593232.

Haines A et al., 2006. Climate change and human health: impacts, vulnerability and public health. Public Health 120: 585-596.

Haines A et al., 2006. Climate change and human health: impacts, vulnerability, and mitigation. The Lancet 367: 2101-2109.

Hansen J et al., 2007. Climate change and trace gases. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences 365: 1925-1954.

Herrera M et al., 2016. Climate change and food safety. In Food safety 2016: 149-160.

Hussain S et al., 2021. An epidemiological survey regarding ticks and tick-borne diseases among livestock owners in Punjab, Pakistan: A one health context. Pathogens 10: Article # 361.

Issar A et al., 2004. Climate Change-Environment and Civilization in the Middle East: Environment and Civilization in the Middle East. Springer Science and Business Media.

Kalkstein et al., 1993. The impact of climate change on human health: some international implications. Experientia 49: 969-979.

Kemp L et al., 2022. "Climate Endgame: Exploring catastrophic climate change scenarios." Proceedings of the National Academy of Sciences 119(34): e2108146119.

Kerr JR and Wilson MS, 2018. Changes in perceived scientific consensus shift beliefs about climate change and GM food safety. PloS one 13: Article # e0200295.

Kim KH et al., 2014. A review of the consequences of global climate change on human health. Journal of Environmental Science and Health Part C 32: 299-318.

Lacetera N, 2019. Impact of climate change on animal health and welfare. Animal Frontiers 9: 26-31.

Luber G and Prudent N, 2009. Climate change and human health. Transactions of the American Clinical and Climatological Association 120: 113-117.

Macklin MG and Lewin J, 2015. The rivers of civilization. Quaternary Science Reviews 114: 228-244.

Mas-Coma S et al., 2008. Effects of climate change on animal and zoonotic helminthiases. Revue Scientifique et Technique 27: 443-457.

McMichael AJ et al., 2006. Climate change and human health: present and future risks. The Lancet 367: 859-869.

McMichael AJ, 2013. Globalization, climate change, and human health. New England Journal of Medicine 368: 1335-1343.

Medlock JM and Leach SA, 2015. Effect of climate change on vector-borne disease risk in the UK. The Lancet Infectious Diseases 15: 721-730.

Miles-Novelo A and Anderson CA, 2019. Climate change and psychology: Effects of rapid global warming on violence and aggression. Current Climate Change Reports 5: 36-46.

Nardone A et al., 2010. Effects of climate changes on animal production and sustainability of livestock systems. Livestock Science 130: 57-69.

Ogden NH, 2017. Climate change and vector-borne diseases of public health significance. FEMS Microbiology Letters 364: Article # 186.

Parry M et al., 1999. Climate change and world food security: a new assessment. Global Environmental Change 9: 51-67.

Patz JA et al., 2005. Impact of regional climate change on human health. Nature 438: 310-317.

Pinto J et al., 2008. Climate change and animal diseases in South America. Revue Scientifique et Technique 27: 599-613.

Reid GK et al., 2019. Climate change and aquaculture: considering adaptation potential. Aquaculture Environment Interactions 11: 603-624.

Reid GK et al., 2019. Climate change and aquaculture: considering biological response and resources. Aquaculture Environment Interactions 11: 569-602.

Rich N, 2018. Losing earth: The decade we almost stopped climate change. New York Times Magazine 1.

Skuce PJ et al., 2013. Animal health aspects of adaptation to climate change: beating the heat and parasites in a warming Europe. Animal 7: 333-345.

Slenning BD, 2010. One health and climate change: linking environmental and animal health to human health. North Carolina Medical Journal 71: 434-437.

Sundstrom JF et al., 2014. Future threats to agricultural food production posed by environmental degradation, climate change, and animal and plant diseases–a risk analysis in three economic and climate settings. Food Security 6: 201-215.

Tirado MC et al., 2010. Climate change and food safety: A review. Food Research International 43: 1745-1765.

Van der Spiegel M et al., 2012. Effects of climate change on food safety hazards in the dairy production chain. Food Research International 46: 201-208.

Venios X et al., 2020. Grapevine responses to heat stress and global warming. Plants 9: Article # 1754.

Vermeulen SJ et al., 2015. Climate change and food systems. Annual review of environment and resources 37: 195-222.

Wheeler T and Braun JV, 2013. Climate change impacts on global food security. Science 341: 508-513.

Yazdi SK and Shakouri B, 2010. The effects of climate change on aquaculture. International Journal of Environmental Science and Development 1: 378-382

Zinsstag J et al., 2018. Climate change and one health. FEMS Microbiology Letters 365: Article # 085.

9

Impact of Plant-Originated Morin Hydrate on Human and Animal Health

AUTHORS DETAIL

Shahid Ali Rajput[1], Aziz Ul Rahman[1], Rana Muhammad Shahbakht[1], Rana Waseem Akhtar[2], Ahsan Anjum[1], Atiq Ali[1], Asghar Abbas[1], Baseer Ahmad[1], Junaid Ali Khan[1], Muhammad Asif Raza[1]* and Aftab Shaukat[3]*

[1]Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef University of Agriculture, Multan, Pakistan
[2]Department of Animal Breeding and Genetics, Faculty of Veterinary and Animal Sciences, Islamia University of Bhawalpur
[3]National Center for International Research on Animal Genetics, Breeding and Reproduction (NCIRAGBR), Huazhong Agricultural University, Wuhan 430070, PR China
*Corresponding author: asif.raza@mnsuam.edu.pk; dr.aftabshaukat@mail.hzau.edu.cn

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INTRODUCTION

Natural bioactive substances are highly sought after because of their pharmacological role in promoting well-being and overall health. Additional research has clarified the function of these natural assets, referred to as "nutraceuticals," beyond "nutrition," emphasizing the importance of daily consumption for the prevention and cure of metabolic ailments (Santana and Macedo 2019). The current increase in the risk of metabolic syndromes, including cancer, heart disease, diabetes, liver and kidney disorders, and their metabolic precursors, such as hyperuricemia and obesity, have threatened the health care system. Physicians are increasingly focusing on disease treatment rather than illness prevention because of the paradigm shift in healthcare policy for multiple factors. As a result, patients often take multiple prescriptions at once, leading to drug interactions and different side effects. Accordingly, there is an immediate need to concentrate on preventing disease through dietary modification, a change in lifestyle and the utilization of medicinal plants (Thakur et al. 2020).

Since the beginning of human civilization, plant and plant products have been used as medicine to avert and cure numerous ailments in the community. A number of plants and extracts high in flavonoids, polyphenols, saponins and carotenes have been studied as potential treatments for a variety of diseases (Kuruvilla 2002). The global functional food and nutraceutical market is expected to grow from $117.04 billion in 2021 to $123.98 billion in 2022 at a compound annual growth rate (CAGR) of 5.9%. Moreover, the market is expected to grow by $156.43 billion in 2026 at a CAGR of 6% (Maleš et al. 2022). Nearly 5000 plant herbs are available for medicinal purposes all over the world (Patwardhan et al. 2005). The WHO report estimates that roughly 75% of people around the globe regularly use herbs derived from plants to treat a variety of diseases and improve their health status (Kuruvilla 2002). To a large extent, herbal medicines and nutraceuticals have gained popularity in health care because of their low toxic effects, simplicity of use and fewer adverse effects compared to synthetic drugs (Rajput et al. 2021).

Morin hydrate (MH) is a naturally occurring phytochemical agent derived from plants such as Rosaceae, Moraceae, and Fagaceae families that are used to avert and cure a variety of ailments in humans and experimental animals (Wen et al. 2019). MH, 3,5,7,2',4'-pentahydroxyflavone, is a bioflavonoid isolated from multiple plants, primarily those in the Moraceae family (Caselli et al. 2016). There is strong evidence to support the notion that MH is a bioactive substance with low toxicity and a wide range of biological and pharmacological characteristics, including radical scavenging (Lee et al. 2017), anti-cancerous (Sivaramakrishnan et al. 2009; Nandhakumar et al. 2012), anti-inflammatory (Yu et al. 2020), antioxidant (Rajput et al. 2021), anti-diabetic (Paoli et al. 2013), anti-arthritis (Dhanasekar et al. 2016), anti-microbial (Farhan 2013), hepatoprotective (Li et al. 2019), nephroprotective (Jonnalagadda et al. 2013), cardioprotective (Verma et al. 2019) and neuroprotective properties (Bachewal et al. 2018). MH's pharmacological properties are mediated by the modulation of numerous signaling pathways such as NF-κB, MAPK (Verma et al. 2019), JAKs/STATs, Keap1/Nrf2 (Chung et al. 2016), ER, mTOR, Wnt/β-catenin, intrinsic and extrinsic pathways (MadanKumar et al. 2014; Hyun et al. 2015).

2. Source of Morin Hydrate

Morin Hydrate is primarily found in plants of the Rosaceae, Moraceae and Fagaceae families. Majorly it occurs in Osage orange, apple skin, fustic, onion, almond, guava, white mulberry, jackfruit, seaweeds, coffee, tea, red wine, cereals and several beverages (Gopal 2013; Rajput et al. 2021).

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3. Chemistry, Absorption and Metabolism of Morin Hydrate

Morin Hydrate (MH) is a flavonol that is distinguished by the presence of a hydroxyl group in the 3-position, and they are composed of 2-phenyl-1-benzopyran-4-one flavone at the backbone. It is a 7-hydroxy flavonol with three more hydroxy substituents located at positions 2', 4', and 5' (Gopal 2013). MH is soluble in methanol and alkaline aqueous solutions, moderately soluble in water emulsion, freely soluble in alcohol, and lightly dissolvable in acetic acid and ether. Moreover, MH is a yellow-colored stable compound and bitter in its pure form. It is a specific isomer of quercetin, but MH and quercetin can be distinguished from one another by their B-ring hydroxylation structures, which are "meta" in MH and "ortho" in quercetin (Rajput et al. 2021). Orally administered MH has a limited bioavailability after a single dose. On the other hand, parental administration results in the highest absorption, despite having some undesirable side effects (Zhang et al. 2015). MH is not very soluble in water when it is glycosylated. Due to its poor solubility in water, MH has a lower bioavailability and less effective therapeutic plasma levels. Furthermore, a glycosidic moiety in the food matrix influences the absorption of flavonoids (Rajput et al. 2021). MH enters the small intestine as a free compound or as a methylated, glycosylated, or sulphated derivative after passing unchanged through the stomach (Choudhury et al. 2017). MH and quercetin are plant-based antioxidant flavonol isomers. Differences influence the pharmacokinetics of MH and quercetin in the hydroxylation patterns on their B-rings, which significantly impact their fate. Previous research demonstrated that quercetin 3-glucosides are efficiently absorbed because they can maintain a reasonable dispersion in the aqueous environment of the intestines and serve as substrates for glycosidases in the brush border region of the small intestine. The glycosidases cannot utilize the other quercetin glycosides, galactosides, or rutinosides as substrates, and pass via small intestine to reach the large intestine. Contrary to MH, it was found that the glucoside forms of quercetin are more easily assimilated than their aglycone pattern. The transport of MH from the bloodstream to the interior of cells has been demonstrated to be an energy-dependent process (Hou et al. 2003). Similarly, an in-vivo study showed a low plasma concentration of MH even after high doses (Li et al. 2019).

Health Perspectives of Morin Hydrate

Morin Hydrate (MH) is well-known for having numerous pharmacological activities (Fig. 1). Numerous in-vivo and in-vitro studies have revealed the ameliorating potential of MH against a variety of fatal diseases (Table 1 and 2). Most importantly, several in-vitro and in-vivo research shows that the main mechanisms underlying its curative potential (anti-inflammatory and anti-oxidative) are well represented (Fig. 2). MH possible therapeutic potential is described in the following subsections.

Antioxidant Potential of Morin Hydrate

Flavonoids are considered potent antioxidants because of their capacity to scavenge free radicals and quench singlet oxygen (Rajput et al. 2019). Therefore, flavonoids have been thoroughly researched to treat oxidative stress-related diseases like cancer, diabetes, ageing, and neurodegenerative disorders. For instance, flavonoid MH has been shown to boost antioxidant- and cell-signaling-related gene expression (Hyun et al. 2015). MH is a powerful antioxidant that inhibits the production of ROS and free radicals. In several in-vitro experiments, MH protects cells against damage from oxidation by modifying the metabolic enzymes and the Nrf2 pathway (Lee et al. 2017). MH's ability to fight free radicals is mostly because presence of dual bond between C2 and C3 as well as the existence of a hydroxyl group (-OH), which activates the C-3 position of the double bond. Moreover, the existence of two hydroxyl groups (-OH) on the B ring's at 2' and 4' positions is believed to contribute to MH's anti-lipid peroxidation potential (Wolfe and Liu 2008). MH alleviates oxidative stress caused by Middle Cerebral Artery Occlusion (MCAO) in rats by lowering MDA levels and enhancing the antioxidant defense system (Sykiotis et al. 2011). Likewise, MH demonstrated tremendous scavenging activity against hydrogen peroxide-induced oxidative damage, as well as improved SOD and decreased ROS accumulation in lung fibroblast (V79-4 Chinese hamster) (Lee et al. 2017). Another study reports that MH protects the cell from oxidative stress by increasing antioxidant enzyme activities and heme oxygenase-1 (Sykiotis et al. 2011). Additionally, MH has been shown to protect pancreatic β-cells from oxidative damage by increasing intracellular antioxidants (SOD, CAT) and activating the Nrf2/ARE signaling (Pachamuthu et al. 2017). All of these studies highlight MH's antioxidant potential via various mechanisms.

Therapeutic Potential of Morin Hydrate against Diabetes

Diabetes affects more than 415 million people globally and is expected to reach 642 million by 2040. Diabetes, if left untreated, causes long-term hyperglycemia, which can lead to hepatic disorders, heart disease, neuropathy, retinopathy, nephropathy and wound healing problems (Al-Lawati 2017). Previous research indicated that administering a high dose of MH to diabetic rats for five weeks could reduce hyperglycemia and inhibit systemic oxidative stress (Proença et al. 2019). Likewise, in the comparison of untreated rats, high-dose MH supplementation reduced fasting glucose and thiobarbituric acid reactive substances in the diabetic rat brain (Paoli et al. 2013).

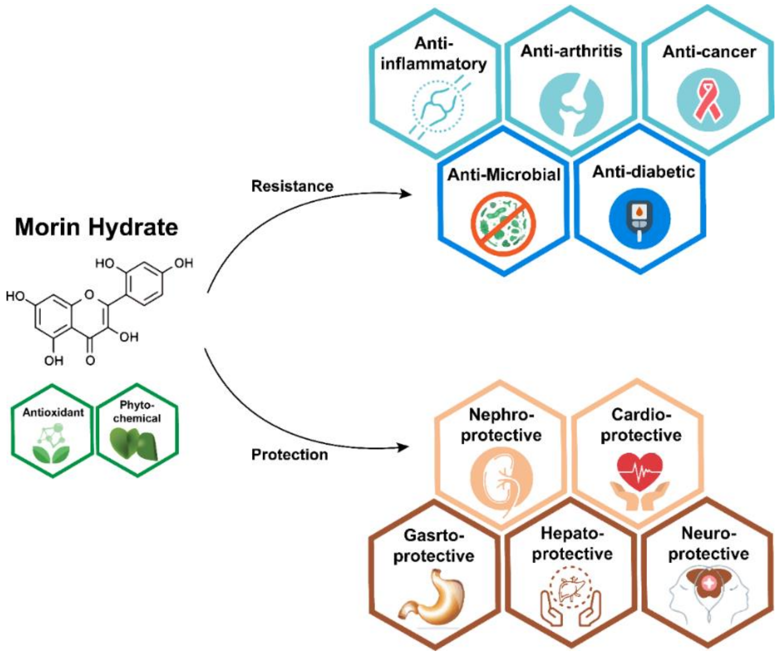

Fig. 1: A mechanistic approach to reveal the pharmacological poteinal of morin hydrate.

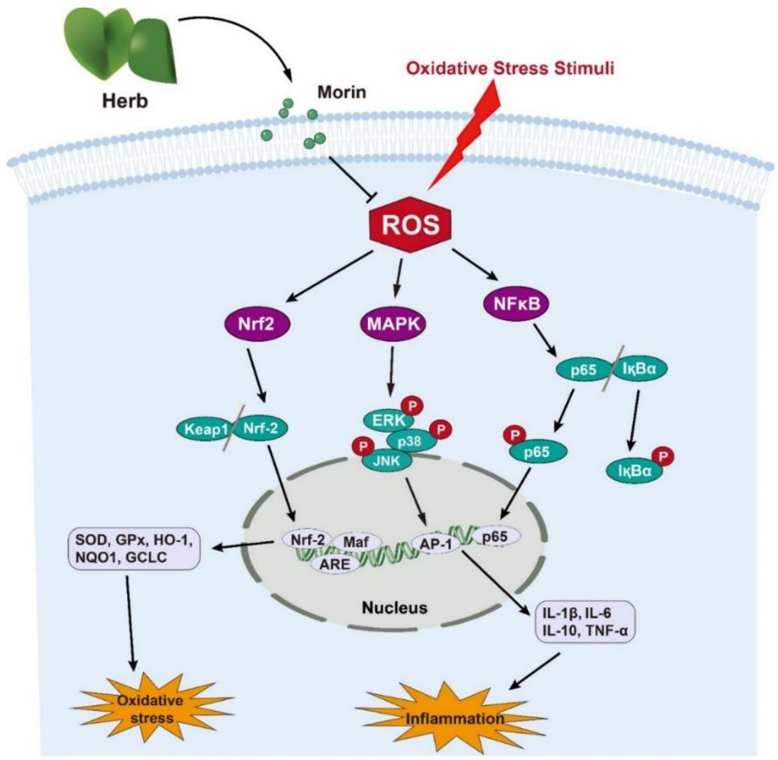

Fig. 2: Schamatic diagram depicts morin hydrates possible pharmacological mechanisms (antioxidant and anti-inflammatory mechanism).

Furthermore, MH may be helpful for the brain by reducing the neurodegenerative effects of diabetes and possibl contributing to the enhancement of memory and learning (Dhingra and Soni 2016). In another study, MH inhibited glucose-stimulated insulin secretion after STZ-induced oxidative stress (Thakur et al. 2020). Additionally, MH treatment significantly alleviates STP-induced diabetes mellitus by reducing glucose levels while improving insulin levels in a murine model. Previous research suggested that the anti-diabetic properties of MH are partly attributed to the

Table 1: Therapeutic potential of Morin Hydrate validated through in-vivo trials.

Study animal	Approach	Duration	Dose	Key findings	Ref.
Wistar rats	Hypertension induced by DOCA-salt	6 weeks	50 mg/kg intragastric	Enhanced antioxidant defense system	Prahalathan et al. 2012
Sprague-Dawley (SD) rats	MCAO-induced cerebral ischemia	7 days	30 mg/kg orally	Neuroprotection through apoptosis and inflammatory response inhibition	Chen et al. 2017
SD rats	Neurotoxicity caused by STZ	2 weeks	50-100 mg/kg p.o.	Neuroprotection action by inhibiting ROS production	Bachewal et al. 2018
SD rats	Chronic constriction injury	14 days	15-30 mg/kg p.o.	Neuropathy is alleviated by preventing neuroinflammation	Komerishettty et al. 2016
C57BL/6 mice	Liver injury induced by CCL$_4$	5 days	50 mg/kg orally	Hepatoprotection via the Nrf2/HO-1 pathway	Li et al. 2019
Albino Wistar rats	ISO-inflicted myocardial damage	28 days	40-80 mg/kg p.o.	Cardioprotection via MAPK/NF-κB pathway inhibition	Verma et al. 2019
Albino Wistar rats	Diabetes mellitus caused by STZ	30 days	25-50 mg/kg orally	Anti-diabetic effects	Vanitha et al. 2014
SD rats	Liver fibrosis induced by CCL$_4$	8 weeks	50 mg/kg orally	Anti-fibrotic effect	Sang et al. 2017
Wistar rats	Liver damage induced by Endosulfan-DMBA	4 weeks	25 mg/kg orally	Xenobiotic metabolizing enzymes are modulated to provide hepatic-protection	Sapmaz et al. 2020
C57BL/6 mice	Fatty liver	8 weeks	100 mg/100g diet	Rescued liver steatosis via inhibiting LXR signaling	Gu et al. 2017
SD rats	Nephrotoxicity caused by gentamycin	15 days	100-200 mg/kg p.o.	Protects kidney	Khattab et al. 2012
ICR mice	kidney injury induced by CP	3 days	20 mg/kg i.p.	Nephroprotection through ER-stress and inflammation suppression	Singh et al. 2018
Swiss albino mice	Reno-hepatic toxicity caused by CP	6 days	50-100 mg/kg intragastric	Reno-hepatic protection through oxidative/nitrosative stress and inflammation reduction	Kandemir et al. 2020
BALB/c mice	OVA-induced asthma	3 days	5 and 10 mg/kg i.p.	Ameliorates airway inflammation	Ma et al. 2016
Rats	Osteoarthritis	28 days	50 mg/kg/d	Anti-osteoarthritis effect via cartilage protection	Chen et al. 2012
Wistar rats	Collagen-induced arthritis	14 days	80 mg/kg	Anti-arthritic effect by inhibiting synovial angiogenesis	Yue et al. 2020
SD rats	Osteoporosis caused by glucocorticoid	5 weeks	5-10 mg/kg i.p.	Protective action against osteoporosis by targeting the MAPK pathway	Wang et al. 2018
Albino SD rats	Gastropathy induced by Indomethacin	4 h	50 mg/kg i.p.	Gastro protective action	Imran et al. 2020
C57B/6J mice	Intranasal lung infection induced by *S. aureus*	8 h	100 mg/kg	Anti-bacterial activity	Wang et al. 2015
BALB/c mice	Mastitis	5 days	20 and 40 mg/kg	Anti-mastitis effect by regulating tight junction proteins	Jiang et al. 2020
Mice model	Parkinson's disease	12 days	5-50 mg/kg i.p.	Anti-Parkinson's disease potential	Lee et al. 2016
Mouse model	Alzheimer's disease	12 weeks	20 mg/kg i.p.	Rescue the Alzheimer's disease	Singh et al. 2018

conservation and shield of pancreatic insulin-producing cells, maintenance of insulin secretion, improvement of glycogen synthesis and enhancement of blood glucose absorption (Vanitha et al. 2014). In rat hepatocytes, MH reduced hyperglycemia by decreasing ROS production and enhancing the antioxidant defense system as well as Bcl-2 and Bax modulation. Previous research suggested that MH could protect the diabetic brain from cellular, functional, and molecular changes (Paoli et al. 2013).

Anti-inflammatory potential of Morin Hydrate

Inflammation plays an important role in the progression of diseases such as neurodegeneration, cardiac disease, metabolic syndrome, and acute pulmonary injury. Inflammation is regulated by a variety of molecules, including pro-inflammatory-inflammatory factors, chemokines, cytokines, enzymes and transcription factors (Rajput et al. 2021). MH inhibit the isoproterenol-induced inflammatory indicators and improves hemodynamic profile in rats by regulating of MAPK signaling (Verma et al. 2019). Lipopolysaccharide (LPS) stimuli increased macrophages' production of pro-inflammatory cytokines and inflammatory markers. Elevated concentrations of these cytokine productions have been linked to chronic inflammation and pathogenesis. Previously, in-vivo and in-vitro research reported that MH significantly rescued the LPS-induced pro-inflammatory and inflammatory markers

Table 2: Therapeutic potential of Morin Hydrate validated through in-vitro trials.

Cell type	Approach	Duration	Dose	Key findings	Ref.
HEK-293	HEK-293 cell stimulated with CP	24 h	10-20 µM	Renoprotection	Singh et al. 2018
HK-2	HK-2 cell stimulated with TM	24 h	50-100 µM	Protecting the proximal tubule by maintaining apoptotic and anti-apoptotic proteins.	Mo et al. 2019
A549	PM2.5-stimulated Human respiratory cells	2 h	10 µM	Shields human respiratory cells and scavenging free radicals	Veerappan et al. 2019
RAW 264.7 macrophage	LPS-stimulated RAW macrophage	24 h	1.25 mM	Anti-inflammatory properties	Fang et al. 2003
Rat hepatocytes	tBHP-stimulated hepatocytes	3 h	5-15 µM	Cellular defense by lowering oxidative stress and activating the Nrf2 pathway	Rizvi et al. 2015
C2C12 myoblasts	H2O2-stimulated myoblasts	6 h	500 µM	Cytoprotective activity by reducing ROS and ERK/HO-1/Nrf2 activation	Liu et al. 2013
RAW264.7 cells	LPS-stimulated	24 h	25-100 µM	Anti-inflammatory effect by inhibiting TREM-1-mediated inflammation	Li et al. 2019
RPE cells	Cigarette smoke extract-stimulated RPE cells	24 h	20 µM	Reduced the risk of age-related macular degeneration	Kim et al. 2019
HLE-B3	Human lens epithelial cells	48 h	50-100 µM	Cytoprotection effect by activation of Nrf2	Park et al. 2013
INS-1E	Pancreatic β cells (INS-1E)	24 h	10-50 µM	Radical scavenging activity	Vanitha et al. 2017
bMEC cells	LPS-stimulated bMEC cells	18 h	50 µM	Anti-mastitis properties by suppression of MAPK pathway	Wang et al. 2016
Murine microglial cells	LPS-stimulated murine microglial cells	16 h	100-300 µM	PKA/HO-1, AKT/MAPK and P13K pathways	Jung et al. 2017
Rat neurons and astrocytes	MPP1-stimulated neurons and astrocytes	24 h	0-100 µM	Parkinson's disease prevention	Lee et al. 2016
LX-2 stellate cells	LX-2 cell stimulated by DEN	24-48 h	50 µM	Anti-fibrotic effect by modulating Wnt/β-catenin signaling	Kumar et al. 2014
HepG2	HepG2 cells stimulated with LPS	12 h	8-32 µg/mL	Hepatoprotection by activating Nrf2 and blocking TLR4/NF-κB	Tian et al. 2017
Human chondrocytes model	Chondrocytes stimulated with IL-1β	24 h	50 µM	Chondroprotection by inhibition of PGE2	Chen et al. 2014
HDFs	Human dermal fibroblast model	24 h	20-50 µM	Effects that shield the skin from UVA radiation exposure	Yong et al. 2018

by the modulation of NF-κB and NLRP3 inflammasome pathway (Yu et al. 2020). Moreover, MH can lessen chronic airway inflammation by reducing ROS and MAPK pathways caused by ovalbumin (OVA) (Ma et al. 2016). Furthermore, MH extract was found to have potent anti-inflammatory activity, as evidenced by decreased phosphorylation of the NF-κB, MAPK, and Protein B (AKT) and pro-inflammatory markers in mouse brain tissue and microglial cells (Jung et al. 2017). Most recently, a study depicted that MH protects the CCL_4-induced liver injury by counteracting the inflammatory response via suppression of NF-κB/TREM-1/TLR4 signaling as well as by regulation of oxidative damage via enhancing the Nrf2 pathway (Sang et al. 2017). From the aforementioned studies, it can be concluded that MH extract has the potential to be used as a possible preventive and therapeutic agent against inflammatory reactions and diseases.

Neuroprotection offered by Morin Hydrate

Morin Hydrate (MH) is a potent antioxidant and anti-inflammatory agent which indirectly achieves neuroprotective effects by modulating enzyme activity or cell apoptosis. MH showed neuroprotective effects against sepsis-associated encephalopathy (Xu et al. 2020). Moreover, oxidative stress is a primary pathogenic mechanism of a number of neurodegenerative diseases, such as Alzheimer's disease (AD), epilepsy, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (Matteo and Esposito 2003). MH provided powerful protection against oxidative stress-related DNA damage and lipid peroxidation in the Alzheimer’s disease (AD) and Parkinson’s disease (PD) models. Previous research reported that MH has both in-vivo and in-vitro neuroprotective effects against PD. The authors hypothesized that MH might function as a possible pharmacological agent for the management and treatment of PD disorders as well as other neurodegenerative diseases (Zhang et al. 2010; Singh et al. 2018). Furthermore, MH depicts protection against brain injury induced by MCAO through the inhibition of ROS level, and inflammatory markers and enhancing the Nrf2 signaling and its downstream molecules (HO-1, GPx, SOD, and CAT) (Y. Chen et al. 2017). In a diabetic neuropathy rat model, researchers discovered that MH protected neurons by lowering oxidative damage and inflammation induced by reactive oxygen species. By suppressing neuroinflammation, oxidative stress, and PARP over-activation, MH also mitigates the symptoms of CCI-induced peripheral neuropathy (Komirishetty et al. 2016). Similarly, MH protects the mice from neuropathological and cognitive damage by focusing on variety of signaling mechanisms. Notably, MH suppressed neuro-inflammation, neuronal apoptosis, and oxidative stress in response to IFA-induced acute neurotoxicity (Du et al. 2016).

Hepatoprotective Effects of Morin Hydrate

The liver is an essential body organ involved in various important functions, including immunity, metabolism, and detoxification (Ramadori et al. 2008). MH reduces liver fibrosis caused by DEN and inhibits the growth of hepatic stellate cells via blocking the Wnt/β catenin pathway (MadanKumar et al. 2014). Likewise, MH showed a shielding role in liver fibrosis induced by DEN as it increases Nrf2 expression and the downstream factors (HO-1 and NQO1). According to previous report, MH could reduce the hepatoxicity induced by DMBA and Endosulfan by regulating the xenobiotic enzymes activities (Sapmaz et al. 2020). A study showed the protective effect of MH and shared that it might reduce fatty liver disease and related metabolic illnesses by blocking the LXR signaling pathway (Gu et al. 2017). These findings imply that MH might be a successful treatment or nutraceutical for hepatic disorders.

Anti-cancerous Properties of Morin Hydrate

Cancer is a major public health concern around the world, referring to a group of diseases caused by abnormal cell growth with intrusive possibilities (Rajput et al. 2021). Cancer is caused by a variety of genetic and environmental factors, including a lack of fruits and vegetables, smoking, insufficient exercise, radiation risk, drinking of alcohol, hereditary factors, and systemic diseases (Ahmadi and Shadboorestan 2016). There is mounting evidence that combining novel bioactive agents with natural and reliable remedial agents is the most effective method for treating a wide variety of human cancers with specific molecular pathways (Zhang et al. 2021). In addition, oxidative stress plays a significant role in the pathogenesis and progression of many different types of cancer. Consequently, the most recent literature has suggested the application of unique antioxidants as a core primary natural curative approach for cancer. MH is one of the most important natural antioxidants because of its potent anti-cancer activity in both in-vivo and in-vitro studies (Sivaramakrishnan et al. 2009; Zhang et al. 2018).

Breast cancer is common in women, and the incidence and death rates are steadily rising.

MH's capability to prevent breast cancer in a DMBA-induced rat model was investigated. The results showed that MH significantly ameliorates the breast carcinoma induced by DMBA via the modulation of the mitochondrial apoptosis pathway, which implied that MH had anti-cancerous activities (Kumar et al. 2014). A study discovered that MH reduced the metastatic in MCF 7 human cancer cell line exposed to TPA by inhibiting MMPs. The molecular mechanism was the regulation of Akt/GSK-3β/c-Fos pathway (Lee et al. 2020). Ovarian tumor has the apical mortality rate among the different types of gynaecological tumors because there is no effective treatment and the available medications have a number of negative side effects when used long-term. MH inhibits the inflammatory reaction and modifies NF-κB signaling to effectively decrease the growth of ovarian cancer and reduce tumor size (Xu and Zhang 2019). In addition, a study reported that MH significantly alleviated the risk of human cervical cancer, with the mechanism being the regulation of the mitochondrial apoptosis pathway (Zhang et al. 2018).

Colon cancer is a major health problem all over the world. MH rescued the occurrence of DMH-induced colon cancer in rats by decreasing (40%) tumor size as compared to the DMH (100%) treated rats (Vennila and Nalini 2009). Moreover, MH significantly inhibits colon carcinogenesis, as evidenced by a significantly lower incidence of colon cancer rate (Sreedharan et al. 2009). Moreover, dietary supplementation of MH alleviates the liver cancer induced by Diethyl nitrosamine (Kumar et al. 2014). In the human lung cancer cell line A549, MH also displayed anti-cancer characteristics by repressing the "oncomires" miR-135b (Yao et al. 2017). Furthermore, a recent study showed that MH activates the Hippo signaling pathway to suppress YAP activity in tongue squamous cell carcinoma cells. This proved that MH has anti-tumor action in TSCC cells (Ji et al. 2018). Additionally, MH regulates cytokine release and suppresses astrocyte activation in rat models of bone cancer pain (Jiang et al. 2017). Melanoma is considered a particularly dangerous form of skin cancers due to its high death rate. Melanoma xenograft model treated with MH displayed decreased tumor size and weight by the regulation of Wnt-3A and stemness markers (Hu et al. 2018). Finally, the accumulated literature suggests that MH has powerful potential to combat various types of cancer via multiple pathways.

Suppression of Miscellaneous Diseases by Morin Hydrate

Plant compounds added to antibacterial preparations have the potential to be effective against multidrug-resistant microbial pathogens because they act on different target sites than conventional antibiotics (Rajput et al. 2021). MH is known as an effective microorganism inhibitor by facilitating the bacterial aggregation, inhibiting biofilm formation, causing cell membrane leakage, and downregulating the PBP2a-mediated resistance mechanism (Yang and Lee 2012). Moreover, MH has been identified as a promising candidate for inhibiting the virulence of *Staphylococcus* (*S.*) *aureus* (Wang et al. 2015). A study reported that MH has preventive properties in influenza-infected mice and blocks influenza virus entry into host cells (Hong et al. 2020). Supplementation of MH safeguards the gastric mucosa by reducing inflammation and apoptosis through the NF-κβ pathway (Sinha et al. 2015). A study reported that administration of micellar nanocarriers loaded with MH remarkably improved the memory of rats under exposure of AlCl3 induced Alzheimer's disease. The authors indicated that MH could be used for the management of Alzheimer's disease (Singh et al. 2018). In addition, there is evidence suggesting that MH could be used as a potential therapeutic agent in the treatment of osteoarthritis in both in-vivo and in-vitro studies (Chen et al. 2012). Previously discovered that MH has a curative effect on osteoporosis and showed that the mechanism was the inhibition of the MAPK pathway (Wang et al. 2018). MH protects rats from isoproterenol-induced myocardial infarction due to its free radical scavenging activity (Verma et al. 2019). The inhalation of cigarette smoke (also known as CS) is a significant contributor to lung inflammation. MH exhibited the shielding effects against mercuric chloride (HgCl2)-induced nephrotoxicity in the rat model (Venkatesan et al. 2010). A study highlights the protective effects of MH against CS-induced lung inflammation. These effects may be mediated by MH's ability to suppress the P13K/ATK/NF-κβ pathway (Cai et al. 2018).

Conclusion

MH plays an important role in the treatment and management of a variety of human and animal pathologies. Extensive in-vitro and in-vivo research over the past few years has uncovered the molecular basis for MH's wide-ranging therapeutic effects. To establish the veracity of these assertions, clinical research on the prospective use of MH in treating and preventing human diseases is required. In light of the above research, morin hydrate could serve as a dietary agent to improve human health and could be helpful in developing a novel drug in the future.

REFERENCES

Ahmadi A and Shadboorestan A, 2016. Oxidative stress and cancer; the role of hesperidin, a citrus natural bioflavonoid, as a cancer chemoprotective agent. Nutrition and cancer 68(1): 29-39.

Al-Lawati JA, 2017. Diabetes mellitus: a local and global public health emergency! Oman medical Journal 32(3): 177.

Bachewal P et al., 2018. Morin exerts neuroprotection via attenuation of ROS induced oxidative damage and neuroinflammation in experimental diabetic neuropathy. Biofactors 44(2): 109-122.

Cai B et al., 2018. Morin attenuates cigarette smoke-induced lung inflammation through inhibition of PI3K/AKT/NF-κB signaling pathway. International immunopharmacology 63: 198-203.

Caselli A et al., 2016. Morin: a promising natural drug. Current Medicinal Chemistry 23(8): 774-791.

Chen WP et al., 2012. Morin inhibits interleukin-1β-induced nitric oxide and prostaglandin E2 production in human chondrocytes. International immunopharmacology 12(2): 447-452.

Chen Y et al., 2017. Morin mitigates oxidative stress, apoptosis and inflammation in cerebral ischemic rats. African Journal of Traditional, Complementary and Alternative Medicines 14(2): 348-355.

Choudhury A et al., 2017. Efficacy of morin as a potential therapeutic phytocomponent: insights into the mechanism of action. International Journal of Medical Research and Health Sciences 6(11): 175-194.

Chung SS et al., 2016. Combination treatment with flavonoid morin and telomerase inhibitor MST-312 reduces cancer stem cell traits by targeting STAT3 and telomerase. International Journal of Oncology 49(2): 487-498.

Dhanasekar C and Rasool M, 2016. Morin, a dietary bioflavonol suppresses monosodium urate crystal-induced inflammation in an animal model of acute gouty arthritis with reference to NLRP3 inflammasome, hypo-xanthine phospho-ribosyl transferase, and inflammatory mediators. European Journal of Pharmacology 786, 116-127.

Dhingra D and Soni K, 2016. Improvement of learning and memory by morin, a flavonoid in young and aged mice. Pharmacologia 7(2): 75-82.

Du Y et al., 2016. Morin reverses neuropathological and cognitive impairments in APPswe/PS1dE9 mice by targeting multiple pathogenic mechanisms. Neuropharmacology 108, 1-13.

Farhan SA, 2013. Study on the interaction of copper (II) complex of morin and its antimicrobial effect. International Journal of Chemical Science 11: 1247-1255.

Gopal JV, 2013. Morin hydrate: botanical origin, pharmacological activity and its applications: a mini-review. Pharmacognosy Journal 5(3): 123-126.

Gu M et al., 2017. Morin, a novel liver X receptor α/β dual antagonist, has potent therapeutic efficacy for nonalcoholic fatty liver diseases. British Journal of Pharmacology 174(18): 3032-3044.

Hong EH et al., 2020. Morin hydrate inhibits influenza virus entry into host cells and has anti-inflammatory effect in influenza-infected mice. Immune Network 20(4): 32.

Hou Y et al., 2003. Profound difference in pharmacokinetics between morin and its isomer quercetin in rats. Journal of Pharmacy and Pharmacology 55(2): 199-203.

Hu J et al., 2018. Morin inhibits proliferation and self-renewal of CD133+ melanoma cells by upregulating miR-216a. Journal of Pharmacological Sciences 136(3): 114-120.

Hyun HB et al., 2015. The flavonoid morin from Moraceae induces apoptosis by modulation of Bcl-2 family members and Fas receptor in HCT 116 cells. International Journal of Oncology 46(6): 2670-2678.

Ji Y et al., 2018. Antitumor activity of the plant extract morin in tongue squamous cell carcinoma cells. Oncology Reports 40(5): 3024-3032.

Jiang W et al., 2017. Morin suppresses astrocyte activation and regulates cytokine release in bone cancer pain rat models. Phytotherapy Research 31(9): 1298-1304.

Jonnalagadda VG et al., 2013. Ameliorative effect of morin hydrate, a flavonoid against gentamicin induced oxidative stress and nephrotoxicity in sprague-dawley rats. International Journal of Pharmacy and Pharmaceutical Sciences 6(1): 852-856.

Jung JS et al., 2017. Suppression of lipopolysaccharide-induced neuroinflammation by morin via MAPK, PI3K/Akt, and PKA/HO-1 signaling pathway modulation. Journal of agricultural and food chemistry 65(2): 373-382.

Komirishetty P et al., 2016. Morin mitigates chronic constriction injury (CCI)-induced peripheral neuropathy by inhibiting oxidative stress induced PARP over-activation and neuroinflammation. Neurochemical research 41(8): 2029-2042.

Kumar RN et al., 2014. Morin accelerates proliferative inhibition via NF-κB mediated transcriptional regulation of apoptotic events during chemical carcinogen induced mammary cancer in rats. Biomedicine and Preventive Nutrition 4(2): 277-290.

Kuruvilla A, 2002. Herbal formulations as pharmacotherapeutic agents. Indian Journal of Experimental Biology 40(1): 7-11.

Lee KS et al., 2020. Inhibition of TPA-induced metastatic potential by morin hydrate in MCF-7 human breast cancer cells via the Akt/GSK-3β/c-Fos signaling pathway. International Journal of Oncology 56(2): 630-640.

Lee MH et al., 2017. Antioxidant and cytoprotective effects of morin against hydrogen peroxide-induced oxidative stress are associated with the induction of Nrf-2-mediated HO-1 expression in V79-4 Chinese hamster lung fibroblasts. International journal of molecular medicine 39(3): 672-680.

Li J et al., 2019. Mechanisms of poor oral bioavailability of flavonoid Morin in rats: From physicochemical to biopharmaceutical evaluations. European Journal of Pharmaceutical Sciences 128: 290-298.

Li X et al., 2019. Morin hydrate inhibits TREM-1/TLR4-mediated inflammatory response in macrophages and protects against carbon tetrachloride-induced acute liver injury in mice. Frontiers in Pharmacology 10: 1089.

Ma Y et al., 2016. Morin attenuates ovalbumin-induced airway inflammation by modulating oxidative stress-responsive MAPK signaling. Oxidative medicine and cellular longevity.

MadanKumar P et al., 2014. Morin ameliorates chemically induced liver fibrosis in vivo and inhibits stellate cell proliferation in vitro by suppressing Wnt/β-catenin signaling. Toxicology and applied pharmacology 277(2): 210-220.

Maleš I et al., 2022. The medicinal and aromatic plants as ingredients in functional beverage production. Journal of Functional Foods 96: 105210.

Matteo V and Esposito E, 2003. Biochemical and therapeutic effects of antioxidants in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Current Drug Targets-CNS and Neurological Disorders 2(2): 95-107.

Nandhakumar R et al., 2012. Morin augments anticarcinogenic and antiproliferative efficacy against 7, 12-dimethylbenz (a)-anthracene induced experimental mammary carcinogenesis. Molecular and cellular biochemistry 364(1): 79-92.

Paoli P et al., 2013. The insulin-mimetic effect of Morin: A promising molecule in diabetes treatment. Biochimica et Biophysica Acta (BBA)-General Subjects 1830(4): 3102-3111.

Patwardhan B et al., 2005. Ayurveda and traditional Chinese medicine: a comparative overview. Evidence-based complementary and alternative medicine 2(4): 465-473.

Proença C et al., 2019. The dipeptidyl peptidase-4 inhibitory effect of flavonoids is hindered in protein rich environments. Food and function 10(9): 5718-5731.

Rajput SA et al., 2021a. Ginsenoside Rb1 prevents deoxynivalenol-induced immune injury via alleviating oxidative stress and apoptosis in mice. Ecotoxicology and Environmental Safety 220: 112333.

Rajput SA et al., 2021b. Luteolin alleviates aflatoxinB1-induced apoptosis and oxidative stress in the liver of mice through activation of Nrf2 signaling pathway. Antioxidants 10(8): 1268.

Rajput SA et al., 2021c. Morin hydrate: A comprehensive review on novel natural dietary bioactive compound with versatile biological and pharmacological potential. Biomedicine and Pharmacotherapy 138: 111511.

Rajput SA et al., 2019. Grape seed proanthocyanidin extract alleviates aflatoxinB1-induced immunotoxicity and oxidative stress via modulation of NF-κB and Nrf2 signaling pathways in broilers. Toxins 11(1): 23.

Ramadori G et al., 2008. Physiology and pathophysiology of liver inflammation, damage and repair. Journal of Physiology and Pharmacology: an Official Journal of the Polish Physiological Society 59: 107-117.

Sang L et al., 2017. Morin enhances hepatic Nrf2 expression in a liver fibrosis rat model. World Journal of Gastroenterology 23(47): 8334.

Santana ÁL and Macedo GA, 2019. Challenges on the processing of plant-based neuronutraceuticals and functional foods with emerging technologies: Extraction, encapsulation and therapeutic applications. Trends in Food Science and Technology 91: 518-529.

Sapmaz C et al., 2020. Modulation of xenobiotic metabolizing enzyme activities in rat liver by co-administration of morin, endosulfan, and 7, 12-dimethylbenz [a] anthracene. Drug and Chemical Toxicology 43(1): 13-21.

Singh M et al., 2018). Development and characterization of morin hydrate-loaded micellar nanocarriers for the effective management of Alzheimer's disease. Journal of Microencapsulation 35(2): 137-148.

Sinha K et al., 2015. Morin protects gastric mucosa from nonsteroidal anti-inflammatory drug, indomethacin induced inflammatory damage and apoptosis by modulating NF-κB pathway. Biochimica et Biophysica Acta (BBA)-General Subjects 1850(4): 769-783.

Sivaramakrishnan V and Devaraj SN, 2009. Morin regulates the expression of NF-κB-p65, COX-2 and matrix metalloproteinases in diethylnitrosamine induced rat hepatocellular carcinoma. Chemico-Biological Interactions 180(3): 353-359.

Sreedharan V et al., 2009. Effect of morin on tissue lipid peroxidation and antioxidant status in 1, 2-dimethylhydrazine induced experimental colon carcinogenesis. Investigational New Drugs 27(1): 21-30.

Sykiotis GP et al., 2011. The role of the antioxidant and longevity-promoting Nrf2 pathway in metabolic regulation. Current Opinion in Clinical Nutrition and Metabolic Care 14(1): 41-48.

Thakur K et al., 2020. Morin as an imminent functional food ingredient: An update on its enhanced efficacy in the treatment and prevention of metabolic syndromes. Food and function 11(10): 8424-8443.

Vanitha P et al., 2017. Morin activates the Nrf2-ARE pathway and reduces oxidative stress-induced DNA damage in pancreatic beta cells. European Journal of Pharmacology 801: 9-18.

Vanitha P et al., 2014. Modulatory effects of morin on hyperglycemia by attenuating the hepatic key enzymes of carbohydrate metabolism and β-cell function in streptozotocin-induced diabetic rats. Environmental toxicology and pharmacology 37(1): 326-335.

Venkatesan R et al., 2010. Effect of Morin on mercury chloride induced nephrotoxicity. Ecoscan 4: 193-196.

Vennila S and Nalini N, 2009. Modifying effects of morin on the development of aberrant crypt foci and bacterial enzymes in experimental colon cancer. Food and Chemical Toxicology 47(2): 309-315.

Verma VK et al., 2019. Role of MAPK/NF-κB pathway in cardioprotective effect of Morin in isoproterenol induced myocardial injury in rats. Molecular Biology Reports 46(1): 1139-1148.

Wang C et al., 2018. Morin protects glucocorticoid-induced osteoporosis through regulating the mitogen-activated protein kinase signaling pathway. Journal of Natural Medicines 72(4): 929-936.

Wang J et al., 2015. Morin hydrate attenuates S taphylococcus aureus virulence by inhibiting the self-assembly of α-hemolysin. Journal of Applied Microbiology 118(3): 753-763.

Wen P et al., 2019. Mulberry: A review of bioactive compounds and advanced processing technology. Trends in Food Science and Technology 83: 138-158.

Wolfe KL and Liu RH, 2008. Structure− activity relationships of flavonoids in the cellular antioxidant activity assay. Journal of Agricultural and Food Chemistry 56(18): 8404-8411.

Xu M and Zhang Y, 2019. Morin inhibits ovarian cancer growth through the inhibition of NF-κB signaling pathway. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents) 19(18): 2243-2250.

Xu X et al., 2020. Morin exerts protective effects on encephalopathy and sepsis-associated cognitive functions in a murine sepsis model. Brain Research Bulletin 159: 53-60.

Yang JY and Lee HS, 2012. Evaluation of antioxidant and antibacterial activities of morin isolated from mulberry fruits (Morus alba L.). Journal of the Korean Society for Applied Biological Chemistry 55(4): 485-489.

Yao D et al., 2017. Morin inhibited lung cancer cells viability, growth, and migration by suppressing miR-135b and inducing its target CCNG2. Tumor Biology 39(10): 1010428317712443.

Yu S et al., 2020. Morin protects LPS-induced mastitis via inhibiting NLRP3 inflammasome and NF-κB signaling pathways. Inflammation 43(4): 1293-1303.

Zhang J et al., 2015. Mechanism of enhanced oral absorption of morin by phospholipid complex based self-nanoemulsifying drug delivery system. Molecular pharmaceutics 12(2): 504-513.

Zhang LX et al., 2021. Resveratrol (RV): A pharmacological review and call for further research. Biomedicine and Pharmacotherapy 143: 112164.

Zhang Q, 2018. Molecular mechanism of anti-cancerous potential of Morin extracted from mulberry in Hela cells. Food and Chemical Toxicology 112: 466-475.

Zhang Z et al., 2010. Morin exerts neuroprotective actions in Parkinson disease models in vitro and in vivo. Acta Pharmacologica Sinica 31(8): 900-906.

10

Human Sleeping Sickness: A Challenge for Health Professionals

AUTHORS DETAIL

Abdullah Azeem[1], Muhammad Kasib Khan[1*], Nida Naazir[1], Muhammad Asad[2], Sundas Afresham[1], Muhammad Usman[1], Maryam Hanif[1] and Muhammad Asif Razzaq[1]

[1]Department of Parasitology, University of Agriculture Faisalabad, Pakistan
[2]Department of Zoology, Division of Science and Technology, University of Education Lahore, Punjab, Pakistan
*Corresponding author: mkkhan@uaf.edu.pk

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INTRODUCTION

Human sleeping sickness is also known as Human African Trypanosomiasis (HAT), the causative agent of the infectious disease is *Trypanosoma brucei* which is transmitted by the blood-sucking tsetse fly (Genus *Glossina*) in Sub-Saharan African countries. There are two types of Human African Trypanosomiasis (HAT): the more prevalent *Trypanosoma brucei gambiense (T. b. gambiense)* - caused west African disease and the less prevalent *Trypanosoma brucei rhodesiense (T. b. rhodesiense)*-caused east African disease (Kennedy 2013).

Human sleeping sickness is the neglected disease in the world and the risk of the disease is associated with conditions like draught, impoverishment, global conflicts, deforestation, instability of the socio-economic status and tsetse flies' exposure to the human and animals. It causes major mortality and morbidity in the human beings and domestic livestock and also threatens millions of the human beings of the 36 Sub-Saharan African countries. Approximately, in the time period of 2016-2020 the human population at risk is 55 million people and *T.b. gambiense* has chronic infections and reported 97% human cases (Venturelli et al. 2022).

Human sleeping sickness disease is a major health issue that can have serious economic consequences. The economic burden of this condition arises not only from the direct costs of treatment, but also from the indirect costs associated with lost productivity and reduced quality of life. Treatment for human sleeping sickness disease can be expensive due to the high cost of medications, diagnostic tests and medical visits. In addition, the costs associated with long-term disability can be significant, particularly for those with severe cases. The indirect costs of this condition are often more difficult to measure but can include an inability to function normally in society or participate in economic activities due to physical or mental impairment. As a result, human sleeping sickness can have a significant economic impact on both individuals and societies. By understanding the economic implications of this condition, public health officials and policy makers can better allocate resources to ensure timely diagnoses and treatment for those affected by human sleeping sickness disease. In addition, research into preventative measures and interventions may help to reduce the economic burden of this condition (Welburn et al. 2009).

Overall, human sleeping sickness disease can have serious and long-lasting consequences for both individuals and societies, including significant economic costs. By understanding the economic implications of this condition and taking steps to mitigate the associated costs, policy makers can ensure that resources are used efficiently to improve patient outcomes (Picozzi et al. 2005).

In the final decade of the 19th century, the name "brucei" honours Sir David Bruce, a Scottish microbiologist to the groundbreaking research on the disease. The infective trypanosomes in *Trypanosoma brucei gambiense* and the main reservoir are the humans while the wild and domestic animals i.e., cattle are the major reservoir of infection of the *T. b. rhodesiense* (Kennedy and Rodgers 2019).

The trypanosome is a single-celled parasite, and it contains 9,000 genes for the variant surface glycoproteins (VSG) and these proteins are present across the surface of the trypanosome and aid in determining the immune specificity. Humans developed some innate defenses against of some trypanosome species. The trypanosomes glycoproteins are present in the human sera which are efficient in protein lysis of the animal trypanosomes which is known as trypanolytic factors (Kennedy and Rodgers 2019).

In the early stages of the disease, the trypanosomes proliferate in the lymph, blood and other body tissues or infected humans experience muscle pain, headache, joint pain, fever, and swelling of the lymph nodes while in the later stages, the trypanosomes invaded in the central nervous system and it typically marked the involvement of the spinal cord and brain, sleep disturbances, extreme lethargy, sensory disturbances, weakness of the motor nerves, coma and if left untreated then it causes frequent death (Fevre et al. 2008).

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Zoonotic Importance of Human Sleeping Sickness Disease

a. Human African Trypanosomiasis

Human African Trypanosomiasis sporadically observed in local populations of Africa and in traveler's population. Humans are main reservoirs of the *Trypanosoma brucei gambiense* while the zoonotic *Trypanosoma brucei rhodesiense* received from the vast range of wild and domestic animals. The disease burden of *T. b. gambiense* – induced the chronic illness in the humans of Western and Central Africa which is fell by 98% (range 27,862 cases in 1998 – 565 cases in 2022) and the *T. b. rhodesiense* was also fell by 84% in human population. Humans living in the endemic areas of the Human African Trypanosomiasis (HAT) developed the defensive immune mechanisms against the Trypanosome species while *T. b. brucei* is pathogenic for the animals (Capewell et al. 2019).

There was a complex host-parasite interaction and divides into two stages: In the early hemolymphatic stage, multiplication of trypanosomes parasite occurs leading to the dissemination of parasite into blood or lymphatic system i.e., liver, heart, spleen and endocrine organs while in the later stage, invasion of the parasite occur across the Blood-Brain Barrier and produced meningoencephalitis and other neurological signs in the body (Venturelli et al. 2022).

b. Animal African Trypanosomiasis

In 1898, Sir David Bruce discovered *T. brucei* in cattle but later in 1909, tsetse flies – blood sucking vector-borne arthropods were identified as trypanosome transmitting vectors. Animal Trypanosomiasis (AT) has a veterinary and public health importance. There several Trypanosomes spp. like in Asia; Animal Trypanosomiasis is caused by *T. evansi* and in South America, AT is affected by zoonotic *T. vivax*, *T. cruzi* and *T. b. evansi* (Malvy and Chappuis, 2011). The African livestock breeds have an immune tolerance mechanism against the Trypanosomes spp. which is known as trypanotolerance and it has the ability to control the parasite replication and its pathological effects. In livestock cattle's, the most pathogenic parasite is *T. congolense* produced extreme morbidity and mortality rates and food and milk products are unusable for the human population while in cattle's, the disease is known as Nagana disease (Venturelli et al. 2022).

Disease Transmission of Human Sleeping Sickness

Trypanosomes are single-celled, hemoflagellate protozoans and the human African Trypanosomiasis (HAT) sub specie *T. b. gambiense* is transmitted by the vector-borne blood-sucking tsetse fly (*Glossina* spp.). The favorable environmental conditions for the tsetse flies are temperature (16 -38 ºC), humidity (50 -80%) and presence of water (Franco et al. 2014). The African trypanosome parasite belongs to the salivarian group of the *Trypanosoma* genus, and the trypanosome structure is delineated as corkscrew-like (Greek word "trypano"; trypanosome derived name from it) (Aksoy et al. 2017). It causes major economic losses to the Sub-Saharan African countries. The disease has two stages: initial hemolymphytic stage called slow-progressing form which is caused by *Trypanosoma brucei gambiense* and trypanosome parasite, lives in the lymphatics and bloodstream while the later stage which is also called fast-progressing form, caused by *Trypanosoma brucei rhodesiense* and trypanosome parasite crosses the Blood-Brain Barrier and resides into the central nervous system (Brun et al. 2010). In some endemic areas of the Africa, changes in climate and land use can reduced the tsetse flies' populations and disrupted the disease transmission. At the inoculation site, development of trypanosomal chancre is formed. The trypanosome parasite enters the human body, multiplies it and transmigration from blood vessels over the epithelium of the choroid plexus, crosses the Blood-Brain Barrier (BBB) and invaded into the central nervous system (CNS). This is the second stage human sleeping sickness. In 2021, 93 percent cases were reported in west and central African countries and *T. b. gambiense* was endemic in these areas (Speidel et al. 2022). The human patient experiences motor nerves weakness, neurological disorders, reduced mental health, abnormalities of the endocrine organs and also causes congenital affects to the vertical transmission and *Trypanosoma brucei* entrusted on tsetse flies for its cyclical transmission while *T. b. rhodesiense* and *T. b. gambiense* can infect human population because these parasites are resistant to a serum protein- apolipoprotein A1 that provokes death in other trypanosomes (Büscher et al. 2017).

Life Cycle

In the mammalian host, the infected tsetse fly injects metacyclic trypanosomes into the skin epithelium tissues and takes blood meal from the skin. Trypanosomes multiply into long, slender proliferating forms in the bloodstream (Szöőr et al. 2020). It transforms into trypomastigotes then moved into other body sites where multiplication occurs in spinal fluid and lymph, and it can infiltrate into the brain parenchyma or central nervous system which is the second stage of sleeping sickness. In the cerebrospinal fluid (CSF), the *T. b. rhodesiense* settled within a few weeks while *T. b. gambiense* take an average of 300 to 500 days (Franco et al. 2014). The replication of the parasite occurred by binary fission and during acute phase, the circulating trypomastigotes in undetectable. The tsetse fly takes blood meal from the human being or other mammals, becomes infected and ingested the bloodstream trypomastigotes from it. It transforms into the replicative procyclic trypomastigotes in the tsetse fly midgut lumen. The procyclic forms accelerated the insect stage-specific glycoproteins EP and GPEET procyclin – showed the

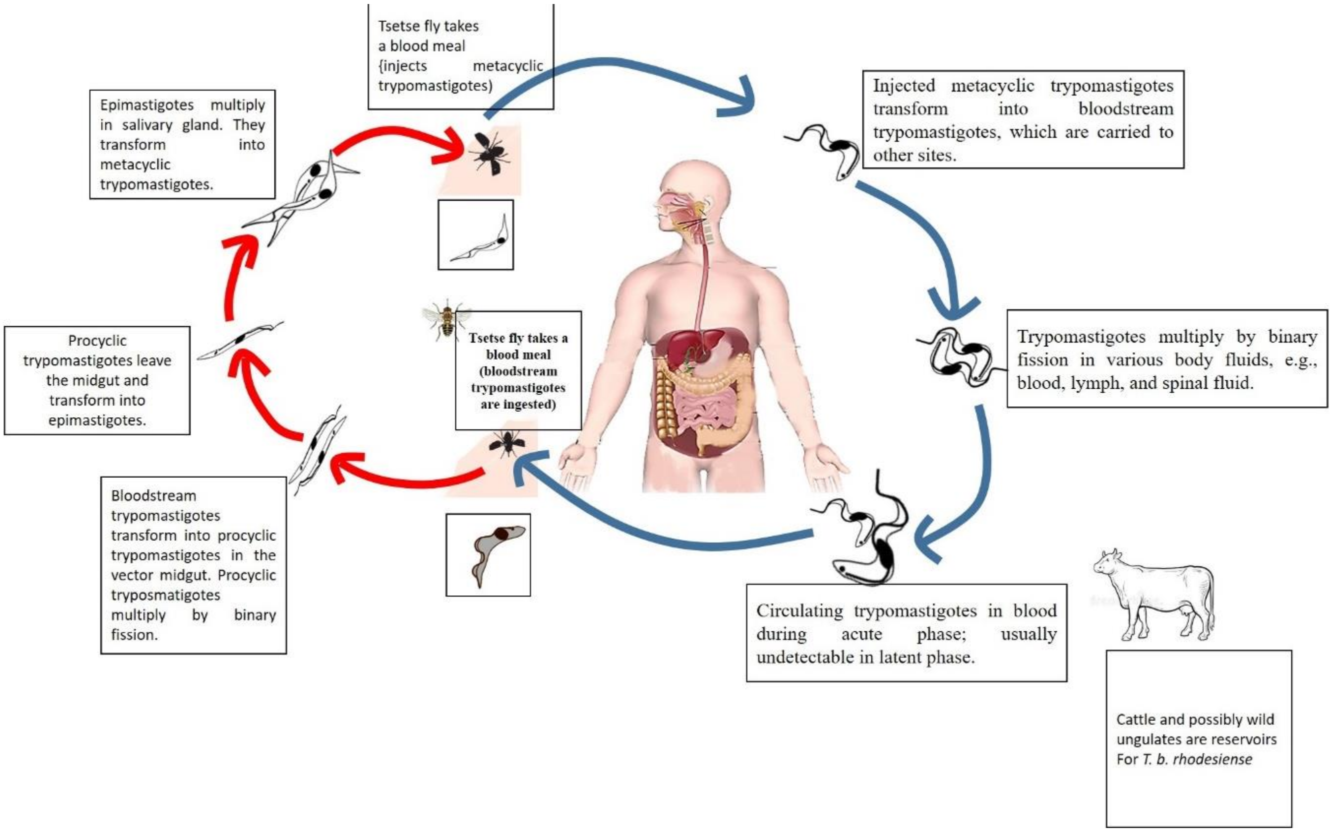
Tsetse fly takes a blood meal {injects metacyclic trypomastigotes)
Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
Tsetse fly takes a blood meal (bloodstream trypomastigotes are ingested)
Bloodstream trypomastigotes transform into procyclic trypomastigotes in the vector midgut. Procyclic tryposmatigotes multiply by binary fission.
Circulating trypomastigotes in blood during acute phase; usually undetectable in latent phase.
Cattle and possibly wild ungulates are reservoirs For T. b. rhodesiense

Fig. 1: Life Cycle of Human African Trypanosomiasis

social motility (Imhof et al. 2014). It left the midgut lumen, altered into epimastigotes stage and resides in the salivary glands, generating the free-swimming metacyclic trypanosomes and transferring into the next mammalian hosts. The cycle completes in the tsetse fly in 3 weeks approximately. During female pregnancy, the parasite can be acquired congenitally if mother is infected (Büscher et al. 2017). Fig. 1 shows the life cycle of Human African Trypanosomiasis.

Signs and Symptoms

HAT sign and symptoms might manifest in the early or late stages. Clinical characteristics make it challenging to differentiate between these stages. Because these two stages can appear to blend into one another, more objective criteria are required to distinguish between them (Kennedy 2013). Signs of the early phases appear 1-3 weeks following the testse fly bite. Malaise, headaches, weariness, sporadic fever, and weight loss are some of these symptoms. As the disease progresses, a number of features can appear, including lymphadenopathy, broadening of the liver or spleen, or both; ophthalmological features like conjunctivitis, keratitis, and iritis; cardiac displays like congestive cardiac failure, pericarditis, and myocarditis; fertility issues like stillbirth, prematurity, abortion, and sterility endocrine dysfunction like gynaecomastia, alopecia, impotence and menstrual abnormalities (Duggan and Hutchinson 1996; de Atouguia and Kennedy 2000; Brun et al. 2010). Typical feature of *T. b gambiense* HAT is Winterbottom's sign that is the occurrence of posterior cervical lymphadenopathy. The findings of systematic analysis of HAT in travelers and immigrants from non-endemic countries revealed that early-stage symptoms such as jaundice, hepatomegaly, or diarrhoea were frequently seen in travelers regardless of the HAT variant they have. This may result in a misdiagnosis of gastroenteritis (Urech et al. 2011). Early HAT symptoms in Uganda include cranial neuropathies, urine incontinence, somnolence, and gait change; these symptoms are rarely consistent with generalized effects of systemic infection on the CNS (MacLean et al. 2010). The late stage of the disease is characterized by a wide range of signs and symptoms. Nearly every part of the nervous system is involved at this stage. These characteristics include aberrant reflexes, disruptions of the motor system, mental problems, and involvement of the sensory system (de Atouguia and Kennedy 2000).

The typical sleep/wake cycle is reversed, there is somnolence during the day, the pattern of sleep is altered, and there are uncontrollable periods of sleep (Buguet et al. 2005). Gait disturbance (22% of cases) is one of the motor disturbances that can develop, along with motor weakness (35% of cases), myelitis, speech difficulties (14% of cases), peripheral motor neuropathy and muscular fasciculation. Some other mental features include anxiety, delirium, hallucinations, lassitude, excessive sexual impulses and in 79% patient's headache was also common in a study (Blum et al. 2006).

Diagnosis

There are 3 steps for the diagnosis of *T. b. gambiense* HAT that include screening, parasitological confirmation, and staging (Lejon et al. 2003; Chappuis et al. 2005). Rapid test for Trypanosomiasis is card Agglutination that is used for majority of HAT control programs (Lumbala et al. 2017). Sensitivity of Card Agglutination test is high (87-98%) on undiluted blood which can leads to a high negative predictive value of a negative test result, as the population usually lies below 5% in the tested population. This low pre-test probability also explains why all individuals with a positive CATT (Card Agglutination Test for Trypanosomiasis) sensitivity on undiluted whole blood or positive CATT with undiluted or mildly diluted (CATT 1:4) serum require parasitological confirmation, despite a reported 95% specificity. In the areas where disease prevalence (> 1%) is high, the treatment of serologically suspected patients with a high CATT titer (≥ 1:16) is acceptable. Serological tests like ELISA and immunofluorescence can also be used and these are more accurate but only use in non-endemic countries. In parasitological confirmation, the blood or cervical lymph node fluid are investigated for the presence of trypanosomes. It is important to use to blood concentration technique because circulating parasites are few. Examination of thick and wet blood smears has low sensitivity. The Capillary tube centrifugation technique or microhaematocrit centrifugation technique are widely used (Marcos et al. 2017). With confirmed HAT the lumbar puncture before Staging by CSF examination is mandatory because treatment considerably differs between two stages that are first and second stage. Presence of high concentration of IgM in CSF also shows the involvement of nervous system (Lejon et al. 2003).

Treatment

For early stage of *T. b gambiense* HAT the first line of treatment is pentamidine which is mostly administered by the intramuscular route but can also be given intravenously. This drug was first used in 1940. Pentamidine is effective but has many potential complications of hypoglycemia or hyperglycemia, hypotension, and prolongation of the QT interval on electrocardiogram (de Atouguia and Kennedy 2000; Brun et al. 2010). For late-stage *T. b gambiense* HAT, Eflornithine, an ornithine decarboxylase inhibitor, has been known to be effective (Kennedy 2008). Oxaboroles is another drug for treatment of late stage of *T. b gambiense* HAT (Jacobs et al. 2011).

Precautions and Control Methods

Precautions and control methods are important for managing the transmission of human sleeping sickness disease. The most effective way to prevent the spread of human African sleeping sickness is through vector control. Insecticide-treated bed nets, insecticide spraying, and land drainage can all be used to reduce the number of tsetse flies in the area. Vector control should be combined with health education campaigns to help people protect themselves from the bites of infected tsetse flies. People who live in areas where sleeping sickness is endemic should also practice safe food storage and disposal practices to avoid putting their food at risk of contamination by infected tsetse flies. Additionally, people living in these areas should use insect repellents to avoid being bitten by these insects. Vaccines are not currently available for human African sleeping sickness, but research is ongoing on the potential vaccine candidates that may prove effective in preventing this potentially fatal disease. Treatment protocols exist for those already infected with sleeping sickness and must be started as soon as possible to increase the patient's chances of survival. Treatment involves a combination of drugs, such as pentamidine and eflornithine depending on the stage and severity of the infection. Careful monitoring must be done during treatment to ensure the effectiveness of the therapy and to identify any potential side effects. With proper control methods, human African sleeping sickness can be prevented and those already infected can receive effective treatment that increases their chances of full recovery. For travelers visiting areas where sleeping sickness is endemic, it is important to take precautionary measures before entering these areas. This includes using insect repellent, wearing long sleeves or pants of light colors that cover exposed arms or legs, avoid standing water where tsetse flies may seek refuge during the day, and sleeping under a bed net impregnated with insecticide. Other recommended measures include disposing of food waste properly to limit tsetse fly attraction and using only bottled water for drinking or brushing teeth. By following these precautionary measures travelers can minimize their risk of contracting human African sleeping sickness (Simarro et al. 2011).

Conclusion

In conclusion, Human African Trypanosomiasis (HAT) is a neglected tropical disease that continues to impact the health and livelihoods of millions of people in sub-Saharan Africa. The disease is caused by the protozoan parasites *T. b. gambiense* and *T. b. rhodesiense*, which are transmitted by tsetse flies. HAT has two stages, the first stage being characterized by nonspecific symptoms such as fever, headache, and joint pain. The second stage, which occurs when the parasites cross the blood-brain barrier, is associated with neurological symptoms such as confusion, seizures, and ultimately coma and death if left untreated. Early diagnosis and treatment are essential for preventing the progression of the disease and reducing mortality rates. Despite advances in diagnosis and treatment, HAT remains a significant public health challenge, particularly in rural areas where access to healthcare is limited. The development of new tools and approaches for diagnosis, treatment and vector control are urgently needed to achieve the WHO goal of eliminating HAT as a public health problem by 2030. Efforts to control HAT have historically focused on screening and treating infected individuals, as well as controlling tsetse fly populations through the use of insecticide-treated traps and targets. In addition to technical and scientific advances, addressing HAT also requires a multisectoral approach that involves strengthening health systems, improving access to healthcare, and addressing social and economic factors that contribute to the spread of the disease.

REFERENCES

Aksoy S et al., 2017. Human African trypanosomiasis control: achievements and challenges. PLoS Neglected Tropical Diseases 11: e0005454.

Blum J et al., 2006. Clinical aspects of 2541 patients with second stage human African trypanosomiasis. Acta Tropica 97: 55-64.

Brun R et al., 2010. Human african trypanosomiasis. The Lancet 375: 148-159.

Buguet A et al., 2005. Sleep structure: a new diagnostic tool for stage determination in sleeping sickness. Acta Tropica 93: 107-117.

Büscher P et al., 2017. Human African trypanosomiasis. The Lancet 390: 2397-2409.

Capewell P et al., 2019. Resolving the apparent transmission paradox of African sleeping sickness. PLOS Biology 17: e3000105.

Chappuis F et al., 2005. Options for field diagnosis of human African trypanosomiasis. Clinical Microbiology Reviews 18: 133-146.

de Atouguia JL and Kennedy PG, 2000. Neurological aspects of human African trypanosomiasis.

Duggan AJ and Hutchinson MP, 1996. Sleeping sickness in Europeans: a review of 109 cases. Journal of Tropical Medicine and Hygiene 69: 124-31.

Fevre EM et al., 2008. The burden of human African trypanosomiasis. PLoS Neglected Tropical Diseases 2: e333.

Franco JR et al., 2014. Epidemiology of human African Trypanosomiasis. Clinical Epidemiology 6: 257.

Imhof S et al., 2014. Social motility of African trypanosomes is a property of a distinct life-cycle stage that occurs early in tsetse fly transmission. PLoS Pathogens 10: e1004493.

Jacobs RT et al., 2011. SCYX-7158, an orally-active benzoxaborole for the treatment of stage 2 human African trypanosomiasis. PLoS Neglected Tropical Diseases 5: e1151.

Kennedy PG and Rodgers J, 2019. Clinical and neuropathogenetic aspects of human African Trypanosomiasis. Frontiers in Immunology 10: 39.

Kennedy PG et al., 2003. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). The Lancet Neurology 12: 186-194.

Kennedy PG, 2008. The continuing problem of human African trypanosomiasis (sleeping sickness). Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society 64: 116-126.

Lejon V et al., 2003. The challenge of Trypanosoma brucei gambiense sleeping sickness diagnosis outside Africa. The Lancet Infectious Diseases 3: 804-808.

Lumbala C et al., 2017. Performance of the SD BIOLINE HAT rapid test in various diagnostic algorithms for gambiense human African trypanosomiasis in the Democratic Republic of the Congo. PloS one 12: e0180555.

MacLean LM et al., 2010. Focus–specific clinical profiles in human african trypanosomiasis caused by Trypanosoma brucei rhodesiense. PLoS Neglected Tropical Diseases 4: e906.

Malvy D and Chappuis F, 2011. Sleeping sickness. Clinical Microbiology and Infection 7: 986-995.

Marcos R et al., 2017. Cell tube block: a new technique to produce cell blocks from fluid cytology samples. Veterinary Clinical Pathology 46: 195-201.

Picozzi K et al., 2005. Sleeping sickness in Uganda: a thin line between two fatal diseases. The BMJ 331: 1238-1241.

Simarro PP et al., 2011. The human African trypanosomiasis control and surveillance programme of the World Health Organization 2000–2009: the way forward. PLoS Neglected Tropical Diseases 5(2): e1007.

Speidel A et al., 2022. Transmigration of Trypanosoma brucei across an in vitro blood-cerebrospinal fluid barrier. iScience - Cell Press 25: 104014.

Szöőr B et al., 2020. A leap into the unknown–early events in African trypanosome transmission. Trends in Parasitology 36: 266-278.

Urech K et al., 2011. Sleeping sickness in travelers-do they really sleep. PLoS Neglected Tropical Diseases 5: e1358.

Venturelli A et al., 2022. Current Treatments to Control African Trypanosomiasis and One Health Perspective. Microorganisms 10: 1298.

Welburn S et al., 2009. Controlling sleeping sickness–a review. Parasitology 136: 1943-1949.

11

Epidemiology and Public Health Risks Associated with Monkey Pox

AUTHORS DETAIL

Sara Ijaz[1*], M. Faizan Elahi Bhatti[1], Mamoona Arshad[1], Ammar Faiz[3], Aiman Mushtaq[2], Sana Shahid[2], Khushbakht Asad[2] and Shama Jamil[4]

[1]Department of Epidemiology and Public health, University of Veterinary and Animal Sciences, Lahore, Pakistan
[2]University of Veterinary and Animal Sciences, Lahore, Pakistan
[3]Department of Meat Science and Technology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]Department of Pathology, University of Veterinary and Animal Sciences, Lahore, Pakistan
*Corresponding author: saraijaz0306@gmail.com

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INTRODUCTION

Monkey pox virus belongs to the genus Orthopoxvirus, subfamily Chordopoxvirinae and family Poxviridae (Peterson and Damon 2014). It causes monkey pox disease which is an emerging zoonotic disease in humans. The virus was first identified in monkeys in a Danish laboratory in 1958, hence the name monkey pox given to the virus (Magnus et al. 1959) . In Zaire (now the Democratic Republic of the Congo, DRC), a 9-month-old boy was found to have the first human case in 1970 (Reynolds et al. 2013).

After smallpox was eradicated in 1980 and smallpox vaccinations were discontinued, monkey pox became the most significant orthopoxvirus harmful for humans. It is thought to be uncommon sporadic zoonotic disease and has a restricted ability to transfer among people (Di Giulio and Eckburg 2004). However, since the smallpox immunization program was discontinued, both the number of reported cases and their geographic distribution have grown. In the DRC, the illness became endemic and life-threatening before spreading to neighboring African nations (Meyer et al. 2002; Rimoin et al. 2010). Before the outbreak of 2022, cases of monkey pox had been reported in a number of western and central African nations. The first cases of monkey pox from outside of Africa were noted in 2003, and nearly all cases in people living outside of Africa and on different continents have been connected to either international travel to nations where the illness is frequently seen or in imported animals. Additionally, the virus's impact across the globe has been emphasized by numerous exportations outside of Africa in recent years ((Peterson and Damon 2014).

The virus can spread among numerous animal species, including monkeys as well as rodents. The animal reservoir, nevertheless, has not been found yet. There is person-to-person transfer, with the lengthiest chain of spread believed to be 6 generations. The febrile prodrome is followed by a phase of skin eruption in the clinical manifestations of monkey pox, which is strikingly analogous to the clinical appearance of smallpox. For monkey pox, lymphadenopathy is a common manifestation. The case fatalities range from 1% to 11% depending on the virus lineage (Malik et al. 2020). Polymerase chain reaction on lesion samples can be used to identify the virus. Given the serological cross-reactivity of the ortho-poxvirus, serological assays and antigen detection do not yield a conclusive diagnosis. When addressing outbreaks, it is essential to pay closer attention to the risks of high-risk patient populations and nosocomial transmission. There is presently no definitive therapy for monkey pox infection, and the case management and effective outbreak response techniques are also not well understood. In order to understand the constantly changing epidemiology of this resurgent ailment, amplified surveillance and case identification of monkey pox cases are crucial tools (Beer and Rao 2019).

Epidemiology and Prevalence

Monkey pox surveillance efforts are not well established, and there is limited data on the prevalence and frequency of the illness. In the DRC, Sierra Leone, Ivory Coast, and Republic of Congo in 1981, serological investigations of people without immunization scars were conducted to determine the incidence of MPXV (monkey pox virus) infection in humans. 15.4% of the 10,300 sera samples tested positive for ortho-poxvirus, with 0.71% of those samples also testing positive for MPXV. The results were inconclusive since later follow-up revealed that some samples were collected from people who had received vaccinations (Jezek et al. 1987).

Between 1981 and 1986, the average yearly cumulative incidence for those living in wooded regions of the north DRC was 1.58 per 10,000 people (Ježek et al. 1988). Between November 2005 and November 2007, a study in the DRC's Sankuru Province revealed a usual yearly cumulative incidence of 5.53 per 10,000. According to this study, monkey pox cases in the same health zone have increased by 20 times since the 1980s (Rimoin et al. 2010). According to a current study of data for the year 2010-2015 from the DRC, there were 0.13 incidences per 10,000 people year on average (Mandja and Gonzalez 2021).

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Seasonal trends of infections are unknown; data during 1970-1980 showed January to March; data of 1981-1986 indicated June to August; data of 2000-2009 revealed July to September; and data of 2010-2015 suggested January to March as the disease emerging time periods of monkey pox cases ((Peterson and Damon 2014).

The first case of the monkey pox disease outbreak in 2022 was discovered on May 7, in the United Kingdom. Since then, a total of nine cases have been confirmed there. Eight of the nine cases had no history of travel and have no connection to the case that was confirmed on May 7 as being related to travel (Ježek et al. 1988).

An additional twenty-six cases have been confirmed in the EU/EEA since May 18 in Italy (1), Sweden (1), France (1), Belgium (2), Spain (7) and Portugal (14) since the UK Health Security Agency (UKHSA) reported cases. Twenty more suspected cases have been reported in Portugal, while 23 more are pending based on test confirmation in Spain (Velavan and Meyer 2022).

Since May 14, there have been 37 confirmed cases of monkey pox worldwide, 26 of which have occurred in EU/EEA nations. Most of the instances are found in young males who identify as MSM (men sex with men). No fatalities have been reported, although two hospitalizations for conditions other than isolation have been noted globally. Additional instances are anticipated, according to health authorities in various counties (Rimoin et al. 2010).

Risk Factors

Most of the cases have involved young males, many of whom self-identify as men who have sexual relationship with other men, and not a single person has a recent travelling history to disease endemic regions. Lacerations on the genitalia or peri-genital region were present in the majority of patients, suggesting that adjacent bodily contact during sexual activity is showing the way the disease is most likely to spread. This is the first instance of chain of dissemination in Europe that have not been linked epidemiologically to endemic areas in Central or West Africa. Additionally, these are the first cases to be recorded among MSM globally (Bunge et al. 2022).

These studies—from the DRC (Fuller et al. 2011; Nolen et al. 2015), the US and the Republic of the Congo (Guagliardo et al. 2020)—reported the risk factors or risk behaviors for developing monkey pox, and they generally confirmed the factors that had already been hypothesized. Sharing a room or bed, residing together, including consuming food or liquids from the same dish are only a few examples of risk behaviors connected to horizontal transmission. (Ježek et al. 1988). Other factors like sleeping outdoors or on the soil, living close to or traveling jungles can increase the chance of exposures to animals and the subsequent risk of monkey pox transmission from animal to human. (Fuller et al. 2011). Unexpectedly, helping with toilet and hygiene, washing clothes, and preparing wild animals for consumption did not significantly increase the risk of contracting monkey pox, but eating duiker was found to be a protective factor (Bunge et al. 2022). In the US monkey pox outbreak of 2003, daily exposure to sick animals or cleaning their cages/bedding were found to be risk factors for contracting the disease. Both substantial and insignificant risk factors were discovered to exist for touching or being bitten by an infected animal (Reynolds et al. 2013).

Signs and Symptoms

The monkey pox disease is brought on by infection with the monkey pox virus, which was first discovered in primates. The virus is primarily spread by rodents. The monkey pox virus has two distinct genetic clades: the central African (Congo Basin) clade and the West African clade. The Congo Basin clade has historically been associated with more severe disease and was thought to be more contagious (Kaler et al. 2022). The disease causes flu-like symptoms such as fever, chills and a rash that may take weeks to go away. Monkey pox has no known cure, however, it typically goes away on its own. When monkey pox first emerged, it was said to have symptoms resembling discrete, typical smallpox. However, one of the main characteristics of monkey pox sickness was lymphadenopathy. However, the disease's typical temporal course and symptoms resembled those of human smallpox. Large respiratory droplets, direct percutaneous or mucosal contact, or viral presence in oro-pharyngeal secretions at the time of rash development were thought to be the main routes of infection. Additionally, anecdotal evidence of apparent trans-placental exposure and infection was presented. Similar to smallpox, patients who needed to be admitted to the hospital had more severe disease trajectories and a higher case fatality rate than outpatients ((Meyer et al. 2002; Rimoin et al. 2010). With the advancement of technology, scientists are now clear that monkey pox can spread from person to person through any close personal contact with monkey pox blisters or scabs, such as during sexual contact, kissing, cuddling, or holding hands, touching clothing, bedding, or towels used by someone with monkey pox, or through a person's cough or sneeze when they are close to others. In many nations where the disease is not common, including the United States, monkey pox is disproportionately afflicting men who have sex with men. Monkey pox can result in serious sickness, including eye involvement, soft-tissue super-infections, and agonizing ano-genital sores, despite not being as fatal as HIV (Fuller et al. 2011). Monkey pox can also be contracted if a person is either bitten or touches the infected animal's fur, skin, blood, bodily fluids, patches, blisters, or scabs, or eats meat that has not been completely prepared. Travel can be the fastest means of spreading an epidemic, as the most recent covid pandemic has made abundantly obvious. Monkey pox's rapid spread from Africa to the US, as well as to many parts of Europe and Asia, is a striking example of the disease's mechanism of transmission (Mandja and Gonzalez 2021).

Pathogenesis

The pathogenesis of human monkey pox and smallpox are strikingly similar. The monkey pox virus has a higher level of lymphadenopathy and can replicate in lymphoid tissue. Monkey pox virus replicates in lymphoid tissue after entry by any route (oropharynx, naso-pharynx, or intradermal). After being released into the bloodstream, the virus first localizes in mononuclear phagocytic cells before localizing in the skin cells. The main organ-systems affected include the testis, ovary, spleen, tonsils, lymph nodes, skin, and mucous membranes. The pancreas and kidney are less often affected organs. The incubation period for monkey pox normally lasts between 6 to 13 days, although it can also be 5 to 21 days. The disease appears around two weeks after infection and exhibits symptoms including fever, headache, general malaise, fatigue and lymph node swelling. After a few days, a rash appears, first on face before moving to other body parts, including the genitalia, conjunctivae, palms of the hands and soles of the feet, oral mucous membranes, and cornea.

The stages of the rash lesions are clearly defined, starting with macules (flattened lesions), progressing to pustules (elevated lesions filled with yellowish fluid), and concluding with scabs that eventually fall off. A few to several thousand lesions may be present. Lesions may combine in severe situations, causing large sections of skin to slough off (Guagliardo et al. 2020).

Life Cycle

Like all other poxviruses, monkey pox virions are large, encapsulated, and "brick-shaped." Each virion contains a core containing a linear, double-stranded DNA genome and the enzymes required for virus uncoating and multiplication. Poxvirus particles initially bind to the host cell membrane via a variety of viral-host protein interactions. In contrast to other mammalian DNA viruses which replicate in nucleus, poxviruses multiply in the cytoplasm in tiny compartments known as 'factories', produced from the rough endoplasmic reticulum (RER) of the host. Despite the fact that they have their own transcriptional machinery, poxviruses depend upon host ribosomes to translate mRNAs into the structural components of the virion and to produce the proteins that rupture the ER membrane of the factory. This rupturing of ER membrane produces tiny, membrane crescents which encapsulate the genome of virions that are assembling. Before leaving the cell via plasma membrane fusion, progeny poxviruses are adorned with extra membranes from the trans-Golgi network (Bunge et al. 2022).

Treatment

There isn't a specific treatment for the monkey pox virus infection till now. However, a number of antiviral drugs used to treat smallpox and other conditions may be helpful to those with monkey pox infection. Supportive treatment and, in some cases, antiviral therapy is used to treat patients with monkey pox (Fuller et al. 2011).

Many monkey pox patients have a mild condition and will recover on their own. However, some individuals might need to take painkillers (e.g., for pain related to proctitis or tonsillitis), stool softeners, topical lidocaine, and/or sitz baths for the conditions like proctitis (Kaler et al. 2022).

Supportive care through hospitalization may be necessary for those who are at risk for dehydration (such as those with nausea, vomiting, dysphagia, or severe tonsillitis), need more intensive pain management, and are dealing with severe disease or complications (Reynolds et al. 2003).

Antiviral Therapy

Monkey pox can be treated with a variety of antivirals. On the basis of dose and safety studies in healthy individuals and animal models, some of these medications were approved for the treatment of smallpox, and it is expected that they will work similarly against monkey pox. Tecovirimat is the preferred medication for this purpose (Guagliardo et al. 2020).

Anti-viral therapy with tecovirimat is indicated for the following groups of patients is suggested:

- Those with a serious condition e.g., haemorrhagic disease, confluent lesions, encephalitis, or other conditions that need hospitalization.
- People who are at a high risk of developing a serious disease, such as young children, people with atopic dermatitis, and with other severe exfoliative skin disorders, pregnant or breastfeeding women, people who have complications like secondary bacterial infections, dehydration, or bronchopneumonia, and those who are immune compromised
- Immune compromised patients, as defined by the Center for Disease Control and Prevention (CDC) in the United States, are typically those who have advanced HIV-1 infection (e.g., CD4 count <200 cells/µl), leukaemia, lymphoma, generalised neoplasms, solid organ transplants, therapy with alkylating agents, antimetabolites, radiation, tumour necrosis factor inhibitors, high-dose corticosteroids, having a hematopoietic cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or a relapse of the disease, or having an autoimmune disease with immunodeficiency as a clinical component.
- Patients with monkey pox infections in often atypical sites (such as the mouth or anogenital region), which are typically accompanied by severe pain (Bunge et al. 2022).

Treatment can begin before test results are available when there is a strong probability that the patient has monkey pox (e.g., when the patient has clinical symptoms that are consistent with monkey pox following a known high-risk exposure). The choice to treat with a different drug, such as cidofovir (or brincidofovir, if available), in the absence of tecovirimat, must be made on an individual basis because the risk of complications is higher with these drugs (e.g., renal failure, electrolyte imbalance) (Petersen BW et al. 2014).

A- Tecovirimat

The drug tecovirimat, also known as TPOXX, is a potent orthopoxvirus protein inhibitor. This orthropox virus proteins are required for the growth of infectious viral particles and important for spreading the disease within a host. Tecovirimat, which can only be obtained via the CDC, was authorized for the small pox treatment in the US in July 2018. The medicine must now be used as part of an expanded access programme run by the CDC because it is only authorized for the smallpox treatment. The dosage of tecovirimat is dependent on the patient's weight; as an example, the dose for people weighing 40 to 120 kg is 600 mg (three capsules) every 12 hours. 14 days are allotted for the course of treatment (Petersen BW et al. 2014).

The drug can be administered through both oral and intravenous (IV) route. Due to the accumulation of an IV formulation ingredient i.e., hydroxypropyl-beta-cyclodextrin, the IV formulation should not be used in cases with severe renal impairments (creatinine clearance [CrCl] <30mL/min) and should be used with precaution in patients with moderate or mild renal disease as well as those under 2 years of age. When the patient is able to take oral drugs, the IV formulation can be switched to oral therapy. Headache, nausea, and abdominal pain are the side effects that are most frequently reported. In an expanded safety trial, it was given to 360 human volunteers, and the adverse effect profile was found to be similar to that of a placebo.

Antiretroviral therapy agent dosage may be affected by possible medication interactions in HIV-positive patients (Reynolds et al. 2003).

Tecovirimat guards against lethal monkey pox virus infections in nonhuman primates and is probably effective against this infection in humans as well. According to case studies, tecovirimat appears to be well tolerated when administered to patients with monkey pox. The one patient who received tecovirimat in a small group of seven patients with monkey pox exhibited no adverse effects and experienced a shorter time of viral shedding and sickness than others (including a few who were administered brincidofovir). A returning tourist from Nigeria and patients who presented with monkey pox during the outbreak that started in May 2022, both received tecovirimat treatment and it proved effective (Petersen BW et al. 2014).

B- Cidofovir/brincidofovir

In June 2021, Brincidofovir was approved to treat smallpox in the United States. It is a pro drug of cidofovir that can be taken orally, and its clinical availability at this moment is unclear. There are few published data about the use of brincidofovir to treat monkey pox. Animal models indicate that it is likely to be an effective treatment for orthopoxvirus infections. In one case study, brincidofovir (200 mg once weekly orally) was administered to three individuals with monkey pox, and all three developed increased liver enzymes, leading to treatment discontinuation (Reynolds et al. 2003).

C- Trifluridine (and vidarabine) Eye Drops or Ointments

In addition to tecovirimat, eye drops or ointments containing trifluridine (or vidarabine) can be used to treat monkey pox lesions that affect the eye or its accessory structures, i.e., the lids. For seven to ten days, drops or creams should be applied every four hours. In cases with eyelid lesions, topical trifluridine or vidarabine have been used for the treatment of vaccinia of the cornea and conjunctiva and to prevent corneal and conjunctival involvement (Reynolds et al. 2003).

Management of Complications

When a patient has monkey pox, secondary bacterial infections can develop. If a patient observes increasing erythema, temperature, or purulence around any lesion, indicating a secondary bacterial skin infection, patient should seek medical attention. The patient should receive sufficient antibiotic treatment in addition to antiviral therapy if a bacterial infection is detected at the time of the initial evaluation or during follow-up visits. Therapy of balanitis or balanoposthitis producing urethral metal obstruction as well as treatment of ocular infection may be included in the management of other complications (Mandja and Gonzalez 2021).

Prevention and Control

The best preventive measure is to keep distance from somebody who has a rash that resembles monkey pox. Although monkey pox is not considered to be a sexually transmitted disease, it is commonly transmitted by prolonged, close physical contact, including sexual contact. If a patient has monkey pox, he/she should avoid sexual activity until all lesions have completely healed, scabs have gone off, and a new layer of skin has grown. Monkey pox can be prevented from spreading with vaccination. However, in light of the present vaccine shortage, a person might want to temporarily alter some habits that could make him/her more susceptible to infection (Mahendra Pal et al. 2017).

Until there is an adequate supply of vaccines, these short-term modifications will aid in slowing the spread of monkey pox (Bunge et al. 2022).

When people are in between getting their first and second doses of the vaccine, it is particularly important to reduce or prevent behaviors that put them at risk of exposure to monkey pox. Two weeks after receiving their second dose of vaccine, their level of protection will be at its peak.

People who have the monkey pox virus might spread it to animals through close contact. Infected animals can also transmit the disease to people. To stop the virus from spreading, people with monkey pox should stay away from pets, domestic animals, and wild animals. For 21 days following the most recent interaction, pets that were in close proximity to a person who had monkey pox symptoms should be kept at home and away from other animals and people. In some instances, it could be necessary to confine and take care of animals that have been exposed to monkey pox away from the house. For example, people who are immune compromised, pregnant women, small kids (under 8 years old), or who have atopic dermatitis or eczema history, should take good care of themselves if they had a direct contact with a patient with monkey pox as they may be at a higher risk of developing serious impacts from monkey pox disease. Smallpox and monkey pox can both be avoided with the JYNNEOS vaccine. During 2022 outbreak, it is the main vaccination being administered. JYNNEOS can be substituted with the ACAM2000 vaccine. It is also approved and helpful in preventing smallpox and monkey pox infections (Mahendra Pal et al. 2017).

Conclusion

The monkey pox virus can spread among numerous animal species, including monkeys as well as rodents. The animal reservoir, nevertheless, has not been found yet. There is person-to-person transfer, with the lengthiest chain of spread believed to be 6 generations. The febrile prodrome is followed by a phase of skin eruption in the clinical manifestations of monkey pox, which is strikingly analogous to the clinical appearance of smallpox. For monkey pox, lymphadenopathy is a common manifestation. The case fatalities range from 1% to 11% depending on the virus lineage. The disease causes flu-like symptoms such as fever, chills, and a rash that may take weeks to go away. Monkey pox has no known cure; however, it typically goes away on its own. The main organ-systems affected include the testis, ovary, spleen, tonsils, lymph nodes, skin, and mucous membranes. The best preventive measure is to keep distance from somebody who has a rash that resembles monkey pox. Although monkey pox is not considered to be a sexually transmitted disease, it is commonly transmitted by prolonged, close physical contact, including sexual contact.

REFERENCES

Beer EM and Rao VB, 2019. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Neglected Tropical Diseases 13(10): e0007791.

Bunge EM et al., 2022. The changing epidemiology of human monkeypox-A potential threat? A systematic review. PLoS Neglected Tropical Diseases 16(2): e0010141.

Di Giulio DB and Eckburg PB, 2004. Human monkeypox: an emerging zoonosis. The Lancet Infectious Diseases 4(1): 15-25.

Fuller T et al., 2011. Using remote sensing to map the risk of human monkeypox virus in the Congo Basin. EcoHealth 8(1): 14-25.

Guagliardo SA et al., 2020. Do monkeypox exposures vary by ethnicity? Comparison of Aka and Bantu suspected monkeypox cases. The American Journal of Tropical Medicine and Hygiene 102(1): 202.

Ježek Z et al., 1988. Human monkeypox: secondary attack rates. Bulletin of the World Health Organization 66(4): 465.

Jezek Z et al., 1987. Smallpox and its post-eradication surveillance. Bulletin of the World Health Organization 65(4): 425.

Kaler J, Hussain A, Flores G, Kheiri S and Desrosiers D, 2022. A Comprehensive Review of Transmission, Pathogenesis, and Manifestation 3;14(7):e26531.

Magnus PV et al., 1959. A pox-like disease in cynomolgus monkeys. Acta Pathologica Microbiologica Scandinavica 46(2): 156-176.

Mahendra Pal, Fisseha M and Venkataramana K, 2017. American Journal of Infectious Diseases and Microbiology. 2017**,** 5(2), 94-99.

Malik YS et al., 2020. Animal-Origin Viral Zoonoses, Springer, Nature.

Mandja BA and Gonzalez JP, 2021. Unveiling the Arcane of an Elusive Virus from the Heart of the African Continent: The Monkeypox. In: Ahmad SI, editor. Human Viruses: Diseases, Treatments and Vaccines: Springer, Cham; pp: 477-499.

Meyer H et al., 2002. Outbreaks of disease suspected of being due to human monkeypox virus infection in the Democratic Republic of Congo in 2001. Journal of clinical microbiology 40(8): 2919-2921.

Nolen LD et al., 2015. Introduction of monkeypox into a community and household: risk factors and zoonotic reservoirs in the Democratic Republic of the Congo. The American Journal of Tropical Medicine and Hygiene 93(2): 410.

Peterson BW and Damon IK, 2014. Orthopoxviruses: vaccinia (smallpox vaccine), variola (smallpox), monkeypox, and cowpox. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 8th Ed., Philadelphia, Elsevier.

Reynolds MG et al., 2003. Spectrum of infection and risk factors for human monkeypox, United States, 2003. Emerging infectious diseases 13(9): 1332.

Reynolds MG et al., 2013. Detection of human monkeypox in the Republic of the Congo following intensive community education. The American Journal of Tropical Medicine and Hygiene 88(5): 982.

Rimoin AW et al., 2010. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. Proceedings of the National Academy of Sciences 107(37): 16262-16267.

Velavan TP and Meyer CG, 2022. Monkeypox 2022 outbreak: an update. Tropical Medicine and International Health.

West Nile Virus- A Neuroinvasive Disease

AUTHORS DETAIL

Muhammad Ali Tahir[1], Kashif Hussain[3], Asghar Abbas[3], Ali Haider[3], Baseer Ahmad[3], Ayesha Ramzan[2], Muhammad Muneeb[2], Shoaib Shafqat[1], Atif Rehman[3], Muhammad Umair Waqas[3], Riffat Yasin[3] and Muhammad Asif Raza[3]

[1] Department of Pathobiology, Faculty of Veterinary Sciences, Bahauddin Zakariya University, Multan
[2] Department of Pathology, University of Agriculture, Faisalabad
[3]Faculty of Veterinary and Animal Sciences, MNS University of Agriculture, Multan
*Corresponding author: kashif.hussain@mnsuam.edu.pk
asghar.abbas@mnsuam.edu.pk

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INTRODUCTION

The world's population is growing at an alarming rate, posing the greatest threat to animals and their environments. Rapid urbanization is a major contributor to global warming and irreversible factors such as increased human-animal interactions, deforestation, and increased resistance to antimicrobials (Mwangi et al. 2016). These factors lead to the transmission and emergence of infectious diseases that primarily affect humans, animals and the environment (Thompson and Polley 2014). About 60% of the emerging humans' diseases are zoonotic in nature, and more than 70% are patented by wildlife species (WHO 2010).

West Nile virus (WNV) is a mosquito-borne neurotropic disease transmitted to humans via infected mosquito bite (Kramer et al. 2007). It is a significant disease that has a major public health concern worldwide (Granwehr et al. 2004; McVey et al. 2015). Firstly, it was reported in 1937 in Uganda. It has been transmitted in the outskirts of the Middle East, Africa, Russia, and Europe for more than 60 years (May et al. 2011). West Nile virus (WNV) belongs to the family Flaviviridae, which includes three genera. It incorporated 3 important viruses including Dengue virus (DENV), yellow fever virus (YFV) and West Nile virus (WNV). Flaviviruses that are transmitted by mosquitoes are largely habitat dependent. The most common is *Culex pipiens*. (Bredenbeek et al. 2003). Furthermore, the WNV virion is approximately 50 nm in diameter and its single copy is embedded within multiple copies of the capsid protein. Its genome consists of 11,000 nucleotides (Klema et al. 2015). WNV consists of the enveloped single-stranded positive-sense RNA genome of the virion. The genome is a single 11 kb open reading frame and lacks a polyadenylation tail at the 3′ ends of the genome. The genome has noncoding regions at both the 3' and 5' ends that form perfect loop structures for replication processes including transcription, translation, and packaging. The virus tends to occupy a membrane envelope and the nucleocapsid contains the viral genome (Khromykh et al. 2001). Moreover, WNV infection has been reported in over 150 species of birds and animals, such as dogs, wolves, horses, goats and squirrels (Nosal and Pellizzari 2003).

Historical Significance

West Nile virus (WNV) was first identified in febrile patients in the West Nile region of northern Uganda in 1937. This patient was seen as part of a pivotal epidemiological study of the yellow fever virus. However, when mice were injected with the patient's serum, viruses with similar characteristics to her two flaviviruses, St. Louis encephalitis virus, and Japanese encephalitis virus, were isolated and shared immunological links with these viruses. These initial experiments with the newly found virus showed that the disease largely impacted the central nervous system (CNS), indicating its neurotropic nature, even though the index patient initially appeared with fever (Smithburn et al. 1940). In-depth descriptions of the epidemiology and ecology of WNV were initially made during several outbreaks in the Mediterranean basin in the early 1950s and 1960s. In 1951, a little village in south of Haifa in Israel had the first known outbreak of WNV. There were 303 residents over there, and disease was confirmed in 123 patients with no fatalities. The bulk of the cases was in children under the age of five. The different clinical characteristics of the illness during this epidemic curve were first thoroughly characterized with the primary symptoms of fever, headache, myalgias, anorexia, stomach discomfort, exanthems and vomiting. Symptoms like lymphadenopathy, angina, and diarrhea were less frequently observed (Murgue et al. 2001).

Between 1951 and 1954, several significant outbreaks in Egypt enhanced the knowledge of ecology, epidemiology, and clinical features of WNV (Taylor et al. 1956). In 1950, WNV was found in the blood of many adolescents, and because of the high seroprevalence, it was detected among

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residents of villages in north of Cairo (Taylor et al., 1956). Extensive studies on WNV have been conducted yet. The research began in 1950 in the Upper Nile Delta region. Investigations included human and animal serosurveys, isolation and characterization of viral vectors, experimental infections of birds, horses, arthropods and humans and ecological evaluations. The study results have greatly improved the understanding of many clinical and epidemiological aspects of the virus. Results of serosurveys showed that WNV was endemic along the Nile, with seroprevalence approaching 60%. Younger children reported more symptomatic disease, but older children and adults appeared to have higher seroprevalence, indicating that WNV was primarily an early childhood infection. Infections were often febrile and self-limited with a low risk of meningitis or encephalitis (Philip and Smadel 1943; Sejvar 2003).

Transmission

Culex mosquitoes act as the main vectors of WNV. However, other mosquito species may also be involved. Mosquito bites are the main cause of WNV infection in vertebrate hosts. More than 300 bird species serve as natural breeding hosts for approximately 100 species of mosquitoes that are the main carriers of WNV. Other animals, including horses and humans, are casual hosts with low viremia and are not involved in the infectious cycle (Fig. 1).

The natural reservoir hosts for WNV include house finches, grackles, sparrows, and corvid species (crows, jays, and magpies). They get WNV from mosquitoes, and birds that eat insects infected with the virus (Davis et al. 2006). Mosquito species differ in their ability to act as disease vectors, feeding on diseased hosts and spreading illness to susceptible hosts (Reisen et al. 2005; Turell et al. 2005). Additionally, the specific mosquito species' host preferences significantly affect the transmission patterns. As an illustration, Culex species often prey on birds, but Aedes and Ochlerotatus species prefer to prey on mammals (Bohart and Wishino 1978; CDC 2003). Some infected mosquitoes don't like to bite birds; this increases the risk of infection in people and other animals. Most mammals do not seem to be involved in the enzootic spread of the virus because when an infection occurs, viremia develops, but it is insufficient for further distribution. Subsequently, these types of hosts may or may not develop the clinical symptoms of the disease, and these hosts are referred as dead-end hosts (Bohart and Wishino 1978).

WNV can potentially spread to humans and animals through non-mosquito-borne routes. Mice exposed to WNV in an investigation transmit the virus through the placenta (Julander et al. 2006). The possibility of WNV spreading directly to the host has been shown by various investigations using experimentally infected animals (Klenk et al. 2004; Although the risk is still incredibly low, the infection has also occurred following the transfusion of blood products contaminated with WNV (Pealer et al. 2003: Stramer et al. 2005). It has also been shown that contact transmission occurs in commercial geese farming. It was believed to be linked to cannibalism and picking at afflicted birds' feathers (Banet-Noach et al. 2003). According to a study, alcoholism was identified as a significant potential cause of WNV infection (Lindsey et al. 2012). WNV infection can also be spread through organ transplants and a blood transfusion from people who have already contracted the virus (Yango et al. 2014). Additionally, the transmission via faeco-oral mode has also been verified (Klenk et al. 2004).

Pathogenesis

While the majority of WNV infections are asymptomatic, seroprevalence studies suggest that 20 to 30 percent of infected individuals have WNV fever and a flu-like disease (Petersen and Marfin 2002; Watson et al. 2004). Nearly, 1 in 150 individuals in a subgroup gets a neuroinvasive condition (Petersen and Roehrig 2001; Weaver and Barrett 2004). Only a few clinical signs of a severe WNV infection include a severe headache, visual abnormalities, muscular weakness, cognitive impairment, tremors, and flaccid paralysis resembling poliomyelitis (Bakri and Kaiser 2004). According to O'Leary et al. (2004), 50% of patients who experience neurologic long-term consequences and 10% of patients who develop neuroinvasive illnesses die (Klee et al. 2004). Elderly people infected with WNV become immunocompromised and are at risk of developing fatal encephalitis (Lim et al. 2011). Understanding the etiology and dissemination mechanisms of WNV has been made possible by rodent models. Initial WNV replication is assumed to happen in Langerhans dendritic skin cells after peripheral injection (Byrne et al. 2001). It causes primary viremia and infection of peripheral organs like the kidney and spleen. The infected cells then travel to lymph nodes. By the end of the first week, WNV has mostly been eliminated from serum and peripheral organs, and only a small percentage of immunocompetent animals have developed CNS infections. A CNS disease comparable to that seen in human WNV cases develops in the infected and damaged brain stem, hippocampus, and spinal cord neurons in infected rodents that die of the infection (Diamond et al. 2003; Arya et al. 2004). In populations of non-neuronal CNS cells in people or animals, WNV infection is not substantially detectable. WNV is eradicated from every tissue compartment in living wild-type mice within two to three weeks of infection. Furthermore, it has been researched that the brains and kidneys of infected hamsters and brains of perforin deficient mice results in chronic viral infection (Shrestha and Diamond 2004; Shrestha et al. 2006; Tesh et al. 2005). A WNV-infected immunosuppressed patient whose viremia was identified for more than 60 days also had a persistent infection (Brenner et al. 2005). Although known about WNV pathogenesis in avian hosts, the virus has been identified in the brains, lungs, livers, hearts, spleens, and kidneys of spontaneously infected crow's and blue jays using histology,

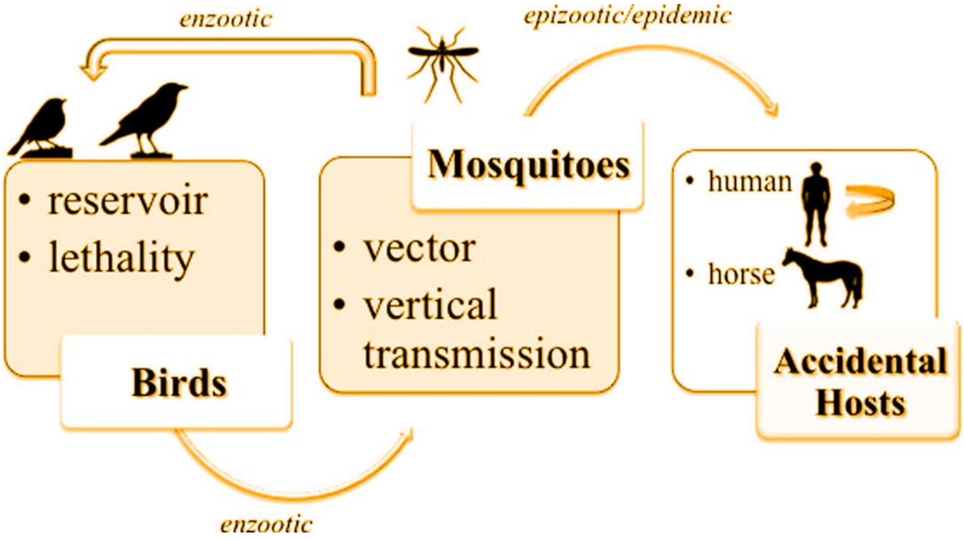

Fig. 1: Infectious cycle of West Nile Virus

reverse transcription-PCR and virologic tests (Panella et al. 2001; Gibbs et al. 2005). Although alterations in endothelial cell permeability caused by tumor necrosis factor-alpha (TNF-α) may make it easier for WNV and other neurotropic flaviviruses to enter the central nervous system (CNS), the exact processes by which they do so remain largely unclear (Wang et al. 2004).

Sometimes, the earlier viral entrance into the brain coincides with greater viral load in serum, so it is probable that WNV infects the CNS at least in parts via hematogenous spread. Additional pathways, such as (i) passive transport or infection across the choroid plexus epithelial cells or endothelium, may contribute to WNV CNS infection (Kramer Hämmerle et al. 2005), which is direct axonal retrograde transport from infected peripheral neurons; (ii) infection of olfactory neurons and spread to the olfactory bulb; (iii) a "Trojan horse" method in which the virus is delivered by infected immune cells that go to the CNS; and (iv). Changes in cytokine levels that may regulate blood brain barrier permeability and infection of blood monocytes and choroid plexus cells have been shown in animal models, even though further research is needed to determine the specific mechanisms of WNV CNS penetration in humans (Samuel and Diamond 2005; Garcia Tapia et al. 2006). Within 24 hours of infection, WNV exhibited large viral yields and progressed cytopathic effects in human brain glioma cells. It is proved that human glioma cells from the CNS might become infected with WNV and are useful for researching the pathophysiology of viruses (Samuel and Diamond 2006). Activation of the innate antiviral immune response pathways is typically the basic cause of pathogenic effects. Double-stranded RNA with viral replication complexes causes transcriptional activation of the interferon-/ (IFN-/) or type-I IFN pathways (Samuel 2001). This work shows that a number of interferon-induced proteins, including IFIT1, IFIT2, IFI27, IFITM1, IFITM2, and G1P2, are activated in glioma cells, validating this pathogenicity mechanism. Glial cells are useful in our inquiry since they are immune cells with CNS origins. Glial cells have the potency to activate the macrophagic potential and immune mediated neuropathologic changes that reflects conditions in the normal CNS host cells. Glial cells can also change the immune response by activating the type-II (IFN-) pathway. Additionally, it was shown that indoleamine 2,3 dioxygenase (INDO) was increased in WNV-infected A172 cells (Koh and Ng 2005).

In neuroinflammatory illnesses, glial cells produce more INDO (Indoleamine), which damages the neurons (Grant and Kapoor 2003). The amplified inflammatory response caused by the overexpression of the pentaxin-related gene (PTX3) is also connected to local tissue damage (Bottazzi et al. 1997). It was also discovered that a collection of apoptosis-causing genes was activated, illuminating the pathways connecting viral replication and apoptosis. These genes include spermidine/spermine N1-acetyltransferase, nuclear factor of kappa light chain gene, tumor necrosis factor superfamily (TNFSF14) and TNF receptor-associated factor (TRAF1) (SAT). WNV propagation is controlled by this highly conserved cellular self-destruction pathway (Chu and Ng 2003).

Life Cycle

The four main stages of the life cycle are attachment/entry, translation, replication and assembly/egress. After attaching to the surface of cells, WNV enters with the help of receptor-mediated endocytosis. Several molecules, including DC-SIGN, e.g., mannose receptors and glycosaminoglycans, have been suggested as West Nile virus receptors (Davis et al. 2006). Endosomal compartment acidification induces a conformational shift in the E protein, fusing the endosomal and viral membranes and releasing the virus nucleocapsid

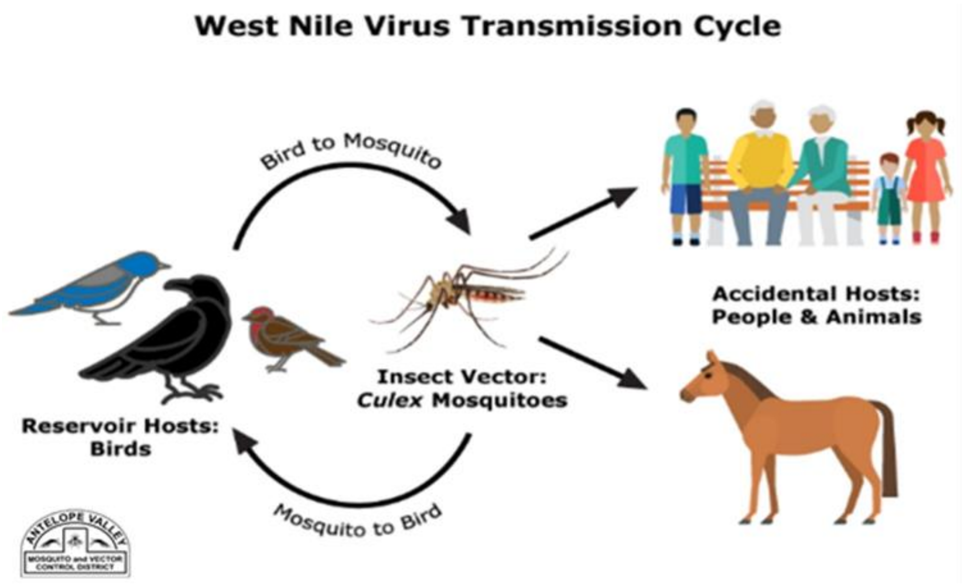
West Nile Virus Transmission Cycle
Bird to Mosquito
Accidental Hosts: People & Animals
Insect Vector: *Culex* Mosquitoes
Reservoir Hosts: Birds
Mosquito to Bird
ANTELOPE VALLEY
MOSQUITO and VECTOR CONTROL DISTRICT

Fig. 2: Transmission cycle of West Nile Virus

into the cytoplasm. After the capsid dissociates, the genome of RNA is copied, and the well-established procedure for viral assembly is started. The ten viral proteins are expressed as a consequence of the translation and processing of the viral polyprotein on intracellular membranes. Cellular and viral proteins duplicate the viral RNA to create numerous copies that may be utilized to create new virions (Rossi et al. 2010). The Golgi network allows the structural proteins to blossom into the cytoplasm once assembled in the endoplasmic reticulum on membranes and joined to the nucleocapsid. Exocytic vesicles carry the virus to the cell surface, where it develops when cellular enzymes break the prM, releasing the mature virus from the cell surface. The function of partly or completely immature flavivirus particles during infection has recently attracted much attention (Colpitts et al. 2012). During maturation, budding and the ineffective cleavage of the prM protein from the virion surface result in the formation of these immature flavivirus particles. According to research, DENV and WNV flavivirus particles, either immature or partly mature, may make up to 40% of the overall virus population in a particular disease (Moesker et al. 2010). When bound by antibodies against the M or E protein, immature WNV particles may be highly infectious and immunogenic in vivo and in vitro. However, these were previously believed to be non-infectious. The Fc receptor on these immature viruses (antibody-bound particles) allows them to infiltrate immune cells and cause productive infection (Colpitts et al. 2012). The transmission cycle of WNV has been illustrated in Fig. 2.

Clinical Signs

The mosquito-borne West Nile virus (WNV), which has the potential to cause catastrophic neurological illness and has achieved worldwide significance, can infect the CNS of a variety of host animals (Hayes et al. 2005). Eighty percent of WNV infections result in asymptomatic patients. The majority of individuals who have symptoms experience an acute, generalized fever known as "West Nile fever" after an incubation period of approximately two to fourteen (2-14) days. Nearly 20% of patients eventually develop WNV fever. In 25 to 30 percent of instances, this self-limiting flu-like virus results in fever, muscular pains, headaches, and digestive problems. There is 25 to 50 percent probability that the body's limbs and trunk will have maculopapular skin irritation (Anderson et al. 2004; Watson et al. 2004; Sejvar 2014).

Regarding neurological symptoms, due to which it is known as "West Nile neuroinvasive illness", there is the presence of encephalitis with the signs of paralysis (Chung et al. 2013). Patients typically experience altered mental conditions, as well as generalized weakness and anomalies of the cranial nerves. In addition to mental disability, encephalitis patients exhibit various extra clinical findings consistent with WNV's ability to affect various brain regions, including the spinal cord. Human infections include the symptoms of everything from fever and muscle aches to infection of the meninges and brain and even death (Petersen et al. 2002). Meningitis caused by the WNV is similar to other viruses' meningitis in clinical indications (Sejvar et al. 2008).

Symptomatic infections can range in severity from mild illnesses resembling the flu to severe brain disorders for which there is no known cure. Many individuals completely recover from fever and viral meningitis. The prognosis is typically benign, and in rare instances, lethargy, headaches, muscle aches, and pain may linger for weeks, months, or even years (Sejvar et al. 2008; Anastasiadou et al. 2011; Murray et al. 2014). More than 1% of infections in human’s result in serious illness, and the most common risk factors include advancing age, immunological suppression, and long-term medical problems, including an increase in blood pressure, diabetes and kidney failure, among others (Bode et al. 2006; Patnaik et al. 2006). Children and people under 30 years are rarely reported to have West Nile neuroinvasive disease (Yim et al. 2004). Older people (over 55 years) and those with weak immune systems due to HIV infection, organ transplants, or recent medication may be more susceptible to the severe signs of WNV infection (Kumar et al. 2004; Pattan et al. 2009). The case-fatality rate varies from 15% to 29% in people over 70 years (Petersen et al. 2002). Homelessness, previous history of cardiovascular illness or kidney diseases, hepatitis C virus and immunosuppression, are all potential causes of brain inflammation and mortality (Murray et al. 2006; Sejvar et al. 2011). The neurological syndrome experiences long-lasting disability. Some patients experience acute muscle weakness and loss of muscle tone (Pealer et al. 2003).

Diagnosis

The diagnosis of WNV depends on the clinical findings and different assays for antibody response (Busch et al. 2008). The European Union case definition states that a person is considered to have a case of human WNV infection if there is the presence of fever, inflammation of the brain along with the inflammation of the meninges, and, according to laboratory standards, a minimum of one requirement must be met to verify the case, such as virus separation or detection of nucleic acid of virus in the cerebrospinal fluid or any other source such as blood. Furthermore, the presence of WNV IgG and a high titer of IgM antibody against WNV are included in the laboratory standards, which are later validated by a neutralization assay (Fox et al. 2006).

Like other viruses, the viral RNA is also detected using several molecular techniques. WNV RNA is found in clinical samples using molecular diagnostic techniques such as amplification techniques, which form the basis for directly detecting acute WNV infection. When symptoms eventually manifest, viral ribonucleic acid is no longer detectable in the blood in about 70–80 percent of infections. According to Chung et al. (2013) and Barzon et al. (2012, 2013), the viral RNA can be detected in urine for a longer time and at a greater titer than in CSF and blood between 2-3 and 14-18 days after infection. WNV antibody detection in serum and CSF is done using immunofluorescence and enzyme immunoassays. It is one of the most popular techniques for determining whether a person has a WNV infection. Because the IgM antibody cannot cross the blood-brain barrier, its existence in the CSF shows an infection in the central nervous system. When symptoms first appear, roughly 80% of patients have shown no longer viremic due to the brief viremic phase's length and the blood's low viral load. Antibodies, specifically IgM, can be found approximately 4 days post-infection, and a few days later, IgG molecules commonly come next (Prince et al. 2005; Tilley et al. 2006; Busch et al. 2008; Prince et al. 2009). A neutralization experiment must follow an enzyme immunoassay or immunofluorescence test to confirm a positive result since flavivirus antibodies might react with one another (cross-reactivity) (Chabierski et al. 2013). There is a specific interaction in the neutralization assay between a laboratory strain of WNV and neutralizing antibodies obtained from patient sera infected with this virus. The virus is bound by neutralizing antibodies, which prevent the virus from attaching to cells and spreading. The serodiagnosis to differentiate different flaviviruses, the plaque-reduction neutralizing test (PRNT) by using live viral particles, is regarded as the "gold standard" (Niedrig et al. 2007; Sanchini et al. 2013).

Diagnosis can also be made using conventional PCR methods. Broad-range PCR-based testing and sequence-independent metagenomic approaches are used to detect the presence of viruses in persons who may be ill when findings from conventional PCR techniques are negative. These methods have made it possible to discover new pathogens in clinical samples and even to recognize infections that were previously unidentified but were crucial to public health (Svraka et al. 2010) Recently, many serological and genetic methods have been utilized to identify WNV infection. These assays must take into account the WNV genome's diversity to distinguish the WNV from other flaviviruses. It is anticipated that new methods will be used for WNV diagnosis as laboratory technology advances and aids in understanding the pathophysiology and diversity of WNV. WNV infection diagnosis is based on various variables, including environmental circumstances, behavioral patterns, and clinical signs. The patient's medical history will provide vital diagnostic hints. For instance, if a patient exhibits clinical signs like fever and headache, one must consider the spread of WNV and its mosquito vector. WNV infection must be considered in endemic locations, particularly during the summer. The patient's medical history should also include exposure to mosquitoes from outside activities. A first physical examination will establish the presence of meningitis, flaccid paralysis, or more serious clinical symptoms such as fever, headache, and myalgia (Sejvar 2014).

Moreover, mosquito bites on the skin will also aid in diagnosis (Rossi et al. 2010). Brain tissue taken during surgery or an autopsy may be used to make the diagnosis. Pathological analysis of mortality revealed widespread neuronal degeneration, perivascular cuffing, and pervasive brain and spinal cord inflammation. These findings result from WNV replication leading to damage, a cytotoxic reaction, and inflammation (Kemmerly 2003).

A- Serological Diagnosis

Checking for WNV-specific IgM antibodies in cerebrospinal fluid or blood typically results in a laboratory diagnosis. A strong indication of the illness is the presence of WNV-specific IgM in the blood and cerebrospinal fluid. The mostly used diagnostic method for identifying WNV is the enzyme-linked immunosorbent test (ELISA). In serum and spinal fluid, the test's sensitivity ranges from 95% to 100%. (Kemmerly 2003). This test is economically feasible and easily accessible in the market. Additionally, serology can be utilized to study immune responses. In CSF samples, reactive lymphocytes or monocytes indicate WNV neurologic infection. More strikingly, a massive influx of polymorphonuclear cells occurs. Neutrophils make up more than 40% of the CSF cells in people with WNV neuroinvasion. testing for plaque neutralization and reduction. IgM antibodies specific to WNV are typically detected 4 to 8 days after the occurrence of the disease and may last for 30 to 90 days. The lack of virus-specific IgM does not necessarily describe the detection of WNV infection if the serum is taken within eight days of disease onset, and tests may be performed on subsequent samples (Lustig et al. 2018). WNV-specific IgM antibodies are not detectable until the end of viremia. Encephalitis and meningitis are shown to occur when a high level of WNV-specific IgM antibodies is present in a person. It may persist for a longer period, from several months to more than one year. It represents the central nervous system infection because Humoral IgM cannot cross the blood-brain barrier. A virus neutralization antibody test should confirm all positive samples. The flaviviruses are antigenically closely related with each other. Recent vaccination against yellow fever or the Japanese encephalitis virus may result in false-positive results on WNV IgM antibody testing. Testing for WNV may cross-react with tests for other infectious diseases, including dengue, St. Louis encephalitis, and other arboviruses. It is still necessary to look for a four-fold increase in neutralizing antibody titer to diagnose WNV infection. It is preferred to employ CDC-defined IgM and IgG ELISA. Plaque-reduction neutralization tests that compare the titers to cross-reacting chemicals may help to identify IgM antibody capture test results that are mistakenly positive. ELISA is more sensitive in case of WNV infections as compared to virus isolation and polymerase chain reaction (PCR) (Kemmerly 2003; De Filette et al. 2012).

B- Nucleic Acid-based Diagnosis

Blood, CSF, and tissue samples may be used for viral cultures and tests to identify viral RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) in the early stages of the disease (Kemmerly 2003). Numerous studies have shown that RT-PCR-based detection is an efficient technique for identifying WNV in clinical samples. Single-tube, real-time PCR is superior to endpoint RT-PCR in a number of ways, including speed, often greater sensitivity, and specificity, and decreased contamination (Lustig et al. 2018). Real-time PCR can also be standardized and allows for the measurement of nucleic acids (De Filette et al. 2012).

C- Miscellaneous Diagnostic Techniques

The WNV antigen may also be recognized by immunohistochemistry (IHC). The lack of WNV infection is not ruled out by negative test results (Kemmerly 2003). In this method, fluorescent protein was used to monitor and detect flavivirus RNA in patients' infected samples using CRISPR-cas13 technology, establishing a viral diagnostic platform with excellent performance and minimal equipment or sample processing requirements (Lustig et al. 2018).

Public Health Importance

WNV is a transboundary disease of One Health concern due to its complex life cycle, which encompasses humans, animals, and the environment (Parkash et al. 2019). Its interactions with reservoir hosts and vectors are necessary for its life cycle. In the end, factors like ambient outside temperature and rainy weather are crucial contributors to the growth of the mosquito population and the strengthening of WNV in susceptible hosts (Baba et al. 2006). In 1998, WNV isolates were found in Israel, demonstrating the virus' propensity for spreading internationally (Banet-Noach et al. 2003). Extreme urbanization, agriculture, and land usage are examples of factors that have diverted from the natural environment and increased the prevalence and incidence of WNV in humans (Kilpatrick 2011). Furthermore, growing crops such as rice need abundant water and a good irrigation system. It causes the mosquito population to increase in the field's stagnant water, resulting in WNV outbreaks (Pradier et al. 2008). Most researchers hypothesized extreme summer temperature was the main culprit in the mosquito population during a heat wave in the U.S. in 1999 (Esser et al. 2019). Moreover, WNV outbreaks are not only associated with mosquito bites but also through organ or blood donation, during lactation, pregnancy, and exposure to infected laboratory instruments (CDC 2002).

WNV incubation periods vary from 3 to 14 days in humans. Febrile illness was reported in 20% of infected people in data reported from New York City (Petersen and Marfin 2002). The signs and symptoms reported in infected individuals include; anorexia, pyrexia, rash, eye swelling, vomiting, myalgia, rash on the body that lasts approximately 3 to 6 days and meningoencephalitis in severe cases. Infected individuals with a previous history of the neurological syndrome have experienced long-lasting disabilities. Some patients may also experience acute muscle weakness and loss of muscle tone (Petersen and Marfin 2002; Pealer et al. 2003).

Conclusion

West Nile virus (WNV) is a neurotropic human pathogen. Its importance as zoonotic disease cannot be neglected due to complex life cycle and global persistence of the mechanical vectors. The fatality rate depends upon the level of infection prevailing in an individual. The lethal disease is very important regarding public health significance and needs appropriate measures for its control.

REFERENCES

Anastasiadou A et al., 2011. Non-neuroinvasive West Nile virus infections during the outbreak in Greece. Clinical Microbiology and Infection 17: 1681-1683

Anderson RC et al., 2004. Punctate exanthem of West Nile Virus infection: report of 3 cases. Journal of the American Academy of Dermatology 51: 820-823.

Arya SC et al., 2004. Spinal Cord Neuropathology in Human West Nile Virus Infection/In Reply. Archives of Pathology and Laboratory Medicine 128: 1210.

Baba MM et al., 2006. The seasonal effect of West Nile Virus in a semi-arid zone, Nigeria. Acad J 1: 31-38.

Bakri SJ et al., 2004. Ocular manifestations of West Nile virus. Current Opinion in Ophthalmology 15: 537-540.

Banet-Noach C et al., 2003. Phylogenetic relationships of West Nile viruses isolated from birds and horses in Israel from 1997 to 2001. Virus Genes 26: 135-141.

Barzon L et al., 2013. Excretion of West Nile virus in urine during acute infection. The Journal of Infectious Diseases 208: 1086-1092.

Barzon Let al., 2013. Large human outbreak of West Nile virus infection in north-eastern Italy in 2012. Viruses 5: 2825-2839.

Bohart RM et al., 1978. Agricultural Sciences Publications, Division of Agricultural Sciences. University of California 42-135.

Bottazzi B et al., 1997. Multimer formation and ligand recognition by the long pentraxin PTX3: similarities and differences with the short pentraxins C-reactive protein and serum amyloid P component. Journal of Biological Chemistry 272: 32817-32823.

Bredenbeek, PJ (2003). A stable full-length yellow fever virus cDNA clone and the role of conserved RNA elements in flavivirus replication. Journal of general virology 84: 1261-1268.

Brenner W et al., 2005. West Nile Virus encephalopathy in an allogeneic stem cell transplant recipient: use of quantitative PCR for diagnosis and assessment of viral clearance. Bone Marrow Transplantation 36: 369-370.

Busch MP et al., 2008. Virus and antibody dynamics in acute West Nile virus infection. The Journal of Infectious Diseases 198: 984-993.

Byrne SN et al., 2001. Interleukin-1β but not tumor necrosis factor is involved in West Nile virus-induced Langerhans cell migration from the skin in C57BL/6 mice. Journal of Investigative Dermatology 117: 702-709.

Centers for Disease Control and Prevention (CDC), 2003. Epidemic/epizootic West Nile virus in the United States: guidelines for surveillance, prevention, and control. Available at: www.cdc.gov/ncidod/dvbid/westnile/resources/ wnv-guidelines-aug-2003.pdf. Accessed September 25, 2007.

Centers for Disease Control and Prevention (CDC), 2002. Intrauterine West Nile virus infection--New York, 2002. Morbidity and mortality weekly report (MMWR) 51: 1135-1136.

Chabierski S et al., 2013. Antibody responses in humans infected with newly emerging strains of West Nile virus in Europe. PLoS One 8: e66507

Chu JJH and Ng ML, 2003. The mechanism of cell death during West Nile virus infection is dependent on initial infectious dose. Journal of General Virology. 84: 3305-3314.

Chung WM et al., 2013. The 2012 West Nile encephalitis epidemic in Dallas, Texas. The Journal of the American Medical Association 310: 297-307

Colpitts TM et al., 2012. West Nile Virus: biology, transmission, and human infection. Clinical Microbiology Reviews 25: 635-648.

Davis LE et al., 2006. West Nile virus neuroinvasive disease. Annals of Neurology 60: 286-300

Davis CW et al., 2006. West Nile virus discriminates between DC-SIGN and DC-SIGNR for cellular attachment and infection. Journal of Virology 80: 1290-1301.

De Filette M et al., 2012. Recent progress in West Nile virus diagnosis and vaccination. Veterinary Research 43: 1-15.

Diamond MS et al., 2003. B cells and antibody play critical roles in the immediate defense of disseminated infection by West Nile encephalitis virus. Journal of Virology 77: 2578-2586.

Esser HJ et al., 2019. Risk factors associated with sustained circulation of six zoonotic arboviruses: a systematic review for selection of surveillance sites in non-endemic areas. Parasites and Vectors 12: 1-17.

Fox JL et al., 2006. Immunoglobulin G avidity in differentiation between early and late antibody responses to West Nile virus. Clinical and Vaccine Immunology 13: 33-36.

Garcia Tapia D et al., 2006. Replication of West Nile virus in equine peripheral blood mononuclear cells. Veterinary Immunology and Immunopathology 110: 229-244.

Gibbs SE et al., 2005. West Nile virus detection in the organs of naturally infected blue jays (Cyanocitta cristata). Journal of Wildlife Diseases 41: 354-362.

Grant R and Kapoor V, 2003. Inhibition of indoleamine 2, 3-dioxygenase activity in IFN-γ stimulated astroglioma cells decreases intracellular NAD levels. Biochemical Pharmacology 66: 1033-1036.

Granwehr BP et al., 2004. West Nile virus: where are we now?. The Lancet Infectious Diseases 4: 547-556.

Hayes EB et al., 2005. Virology, pathology, and clinical manifestations of West Nile virus disease. Emerging Infectious Diseases 11: 1174-1179.

Patnaik JL et al., 2006. Follow-up of 2003 human West Nile virus infections, Denver, Colorado. Emerging Infectious Diseases 12: 1129–1131,

Julander JG et al., 2006. West Nile virus infection of the placenta. Virology 347: 175–182.

Kemmerly SA, 2003. Diagnosis and treatment of West Nile infections. Ochsner Journal 5: 16-17.

Khromykh AA et al., 2001. Essential role of cyclization sequences in flavivirus RNA replication. Journal of Virology 75: 6719-6728.

Kilpatrick AM., 2011. Globalization, land use, and the invasion of West Nile virus. Science 334: 323-327.

Klee AL et al., 2004. Long-term prognosis for clinical West Nile virus infection. Emerging Infectious Diseases 10: 1405.

Klema VJ et al., 2015. Flaviviral replication complex: coordination between RNA synthesis and 5′-RNA capping. Viruses 7: 4640-4656.

Klenk K et al., 2004. Alligators as West Nile virus amplifiers. Emerging Infectious Diseases 10: 2150-2155.

Koh and Ng (2005). Molecular mechanisms of West Nile Virus pathogenesis in brain cells.

Kramer LD et al., 2007. West nile virus. The Lancet Neurology 6: 171-181.

Kramer Hämmerle S et al., 2005. Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. Virus Research 111: 194-213.

Kumar D et al., 2004. A seroprevalence study of West Nile virus infection in solid organ transplant recipients. The American Journal of Transplantation 4: 1883-1888.

Lim SM et al., 2011. West Nile virus: immunity and pathogenesis. Viruses 3: 811-828.

Lindenbach BD, 2007. Flaviviridae: the viruses and their replication. Fields Virology 2007: 1102-1153.

Lustig Y et al., 2018. Surveillance and diagnosis of west nile virus in the face of flavivirus cross-reactivity. Frontiers in Microbiology 9: 2421.

May FJ et al., 2011. Phylogeography of West Nile virus: from the cradle of evolution in Africa to Eurasia, Australia, and the Americas. Journal of Virology 85: 2964-2974.

McVey DS et al., 2015. West Nile virus. Revue scientifique et technique (International Office of Epizootics) 34: 431-439.

Moesker B et al., 2010. Characterization of the functional requirements of West Nile virus membrane fusion. Journal of General Virology 91: 389-393.

Murgue B et al., 2001. West nile in the mediterranean basin: 1950-2000. Annals of the New York Academy of Sciences 951: 117-126.

Murray K et al., 2006. Risk factors for encephalitis and death from West Nile virus infection. Epidemiology and Infection 134: 1325-1332.

Murray KO et al., 2014. Survival analysis, long-term outcomes, and percentage of recovery up to 8 years post-infection among the Houston West Nile virus cohort. PLoS One 9: 102953

Mwangi W et al., 2016. One health: addressing global challenges at the nexus of human, animal, and environmental health. PLoS Pathogens 12: 1005731.

Niedrig M et al., 2007. Comparison of ELISA and immunoassays for measurement of IgG and IgM antibody to West Nile virus in human sera against virus neutralisation. The Journal of Virological Methods 139: 103-105

Nosal B and Pellizzari R, 2003. West Nile virus. Canadian Medical Association Journal 168: 1443-1444.

O'Leary DR et al., 2004. The epidemic of West Nile virus in the United States, 2002. Vector-borne and Zoonotic Diseases 4: 61-70.

Panella NA et al., 2001. Comparative West Nile virus detection in organs of naturally infected American crows (Corvus brachyrhynchos). Emerging Infectious Diseases 7: 754.

Parkash V et al., 2019. West Nile virus infection in travelers returning to United Kingdom from South Africa. Emerging Infectious Diseases 25: 367.

Pattan SR et al., 2009. West Nile fever: an overview. American Journal of Biomedical Science and Research 1: 33–48.

Pealer L et al., 2003.Transmission of West Nile virus through blood transfusion in the United States in 2002. The New England Journal of Medicine 349: 1236-1246.

Petersen LR and Marfin AA, 2002. West Nile virus: a primer for the clinician. Annals of Internal Medicine 137: 173-179.

Petersen LR and Roehrig JT, 2001. West Nile virus: a reemerging global pathogen. Revista Biomédica 12: 208-216.

Philip CB and Smadel JE, 1943. Transmission of West Nile virus by infected Aedes albopictus. Proceedings of the Society for Experimental Biology and Medicine 53: 49-50.

Prince HE et al., 2009. Frequency of missed cases of probable acute West Nile virus (WNV) infection when testing for WNV RNA alone or WNV immunoglobulin M alone. Clinical and Vaccine Immunology 16: 587-588.

Prince HE et al., 2005. Developkleinment and persistence of West Nile virus-specific immunoglobulin M (IgM), IgA, and IgG in viremic blood donors. Journal of Clinical Microbiology 43: 4316-4320.

Pradier S et al., 2008. Land cover, landscape structure, and West Nile virus circulation in southern France. Vector-Borne and Zoonotic Diseases, 8(2), 253-264.

Reisen WK et al., 2005. Avian host and mosquito (Diptera: Culicidae) vector competence determine the efficiency of West Nile and St. Louis encephalitis virus transmission. Journal of Medical Entomology 42: 367–375.

Rossi SL et al., 2010. West Nile virus. Clinics in Laboratory Medicine 30: 47-65.

Samuel CE, 2001. Antiviral actions of interferons. Clinical Microbiology Reviews 14: 778-809.

Samuel MA and Diamond MS, 2005. Alpha/beta interferon protects against lethal West Nile virus infection by restricting cellular tropism and enhancing neuronal survival. Journal of Virology 79: 13350-13361.

Samuel MA and Diamond MS, 2006. Pathogenesis of West Nile Virus infection: a balance between virulence, innate and adaptive immunity and viral evasion. Journal of Virology 80: 9349-9360.

Sanchini A et al., 2013. Second international diagnostic accuracy study for the serological detection of West Nile virus infection. PLOS Neglected Tropical Diseases 7: 2184.

Sejvar JJ et al., 2008. Neurocognitive and functional outcomes in persons recovering from West Nile virus illness. Journal of Neuropsychology 2: 477-499.

Sejvar JJ et al., 2011. Primary causes of death in reported cases of fatal West Nile Fever, United States, 2002-2006. Vector Borne Zoonotic Diseases 11: 161–164.

Sejvar JJ, 2014. Clinical manifestations and outcomes of West Nile virus infection. Viruses 6: 606–623.

Sejvar, J.J 2005. West Nile virus–associated flaccid paralysis. Emerging infectious diseases 11: 1021.

Sejvar JJ, 2003. West nile virus: an historical overview. Ochsner Journal 5: 6-10.

Shrestha B and Diamond MS, 2004. Role of CD8+ T cells in control of West Nile virus infection. Journal of Virology 78: 8312-8321.

Shrestha B et al., 2006. CD8+ T cells require perforin to clear West Nile virus from infected neurons. Journal of Virology 80: 119-129.

Smithburn KC et al., 1940. A neurotropic virus isolated from the blood of a native of Uganda. American Journal of Tropical Medicine 20: 471-472.

Stramer SL et al., 2005. West Nile virus among blood donors in the United States, 2003 and 2004. The New England Journal of Medicine 353: 451-459.

Svraka S et al., 2010. Metagenomic sequencing for virus identification in a public-health setting. Journal of General Virology 91: 2846-2856.

Taylor RM et al., 1956. A study of the ecology of West Nile Virus in Egypt. The American Journal of Tropical Medicine and Hygiene 5: 579-620.

Tesh RB et al., 2005. Persistent West Nile virus infection in the golden hamster: studies on its mechanism and possible implications for other flavivirus infections. The Journal of Infectious Diseases 192: 287-295.

Thompson RA and Polley L, 2014. Parasitology and one health. International Journal for Parasitology: Parasites and Wildlife 3: 1

Tilley PAG et al., 2006. Nucleic acid testing for West Nile virus RNA in plasma enhances rapid diagnosis of acute infection in symptomatic patients. The Journal of Infectious Diseases 193: 1361-1364.

Turell MJ et al., 2005. An update on the potential of North American mosquitoes (Diptera: Culicidae) to transmit West Nile Virus. Journal of Medical Entomology 42: 57-62.

Bode V et al., 2006. West Nile Virus disease: a descriptive study of 228 patients hospitalized in a 4-county region of Colorado in 2003. Clinical Infectious Diseases 42: 1234–1240.

Wang T et al., 2004. Toll-like receptor 3 mediates West Nile virus entry into the brain causing lethal encephalitis. Nature Medicine 10: 1366-1373.

Watson JT et al., 2004. Clinical characteristics and functional outcomes of West Nile virus fever. Annals of Internal Medicine 141: 360-365.

Yango A.F 2014. West Nile virus infection in kidney and pancreas transplant recipients in the Dallas-Fort Worth Metroplex during the 2012 Texas epidemic. Transplantation. 97 953-957.

Weaver SC and Barrett AD, 2004. Transmission cycles, host range, evolution and emergence of arboviral disease. Nature Reviews Microbiology 2: 789-801.

World Health Organization Asia Pacific Strategy for Emerging Diseases, 2010. Manila: WHO Regional Office for the Western Pacific.

Yim R et al., 2004. Spectrum of clinical manifestations of West Nile virus infection in children. Pediatrics 114: 1673-1675.

COVID-19 Pandemic: Its Public Health Concern and Economic Outcomes in Pakistan and Future Impact

AUTHORS DETAIL

Maria Jamil[1], Aisha Khatoon[1*], Muhammad Kashif Saleemi[1*], Al-Hafiza Shafia Tehseen Gul[1], Muhammad Imran[1], Wafa Majeed[2], Ashiq Ali[1], Muhammad Yasir Nawaz[1] and Aftab Shaukat[3]

[1]Department of Pathology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]Department of Pharmacy, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[3]National Centre for International Research on Animal Genetics, Breeding and Reproduction (NCIRAGBR), Huazhong Agriculture University, Wuhan 430070, China
*Corresponding author: aisha.khatoon@uaf.edu.pk; drkashif313@gmail.com

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INTRODUCTION

The epidemic of coronavirus infection 2019 has serious impact on national as well as global economy. Several enterprises are challenging with this issues with firm degree of losses. The major problems include decline in demand and disturbance of supply chain, export order cancellation, shortage of raw material and interruption of transportation. It is now clear that enterprises around the world are facing the significant effects of COVID-19 outbreaks on their business. Main victims of COVID-19 outbreak are micro small and medium sized enterprises (MSMEs) as compare to larger enterprises, because MSMEs don't having enough resources and are not ready for such disturbances likely to go longer than expected (Prasad et al. 2015; Bartik et al. 2020).

According to United Nation Conference on Trade and Development (UNCTAD 2020a), currently, Pakistan might be at the great threat by the COVID-19 pandemic. Thus this justify the requirement to analyze the effects of COVID-19 eruption on MSMEs operative especially in Pakistan. Moreover, the constant pandemic disaster will rigorously obstruct the operation of these business, as MSMEs were mainly reliant on the cash economy that had been seriously disturbed by the pandemic (Williams and Schaefer 2013).

World Health Organization has already stated the COVID-19, as a pandemic. In the initial phase of 2020, the whole world was facing this pandemic that was truly a black swan event. In Pakistan on daily basis 6825 cases were reported on 14 June, 2020 and 213 cases were the lowest official number which were reported on 30 August, 2020. On second week of October, 2020 second COVID-19 wave was started and on 6 December, 2020 maximum number of cases i.e., 3795 cases were reported from Pakistan. As of increasing number of cases, the maximum number remained close to 1000 cases till February 2021. Third COVID-19 wave in Pakistan was officially identified to have started in the second week of March 2021. On March 2021 number of cases were enhancing at an infection rate of 8% and CFR was 1.2%. Total number of cases was >600 thousand and was estimated to enhance due to increase in infection rate as well as outbreak of new variant of virus. It was worth mentioning here that significant part of Pakistan's labor force was working in informal sectors, thus it was understood that due to this fact Pakistan's population was seriously affected by the closure of economic activities, idleness and scarcity was likely to enhance manifold if the condition continues for longer period (Pakistan Economic Survey 2020-2021). The Government relief's package mediated to decline mental stress of community and enhance the worth of their lives. IMF stated that during June 2021 Pakistan's GDP was bounced back at 4% growth. Fig. 1 and Fig. 2 analyzes the COVID-19 impact on the working population of Pakistan.

Impacts of COVID-19 on the Worldwide Economy

The consequences of the COVID-19 infection on community and economy may be observed from the lockdown of cities worldwide, restriction of labor mobility, bans on travel, airline suspension and significantly drop of the economy. COVID-19 disaster became a worldwide issue from 21 February to 24 March, 2020 and still the number of infected persons were rising promptly on daily basis. It was expected that COVID-19 outbreak had main effects on worldwide GDP growth rate (Word Economic 2020). Due to the global outbreak of COVID-19, the worldwide GDP growth rate was probably to be infected ranging from 2.4-4.9% (ADB 2020). Moreover, it had also been expected that COVID-19 pandemic may result in worldwide foreign direct asset to shrink by 5-15% (UNCTAD 2020b). Additionally, UNCTAD report explore that the world requires a funding package of upto 2.5 $ trillion to manage such huge destruction (UNCTAD 2020a). Therefore, on the basis of this statistics, the recent worldwide disaster would probably be

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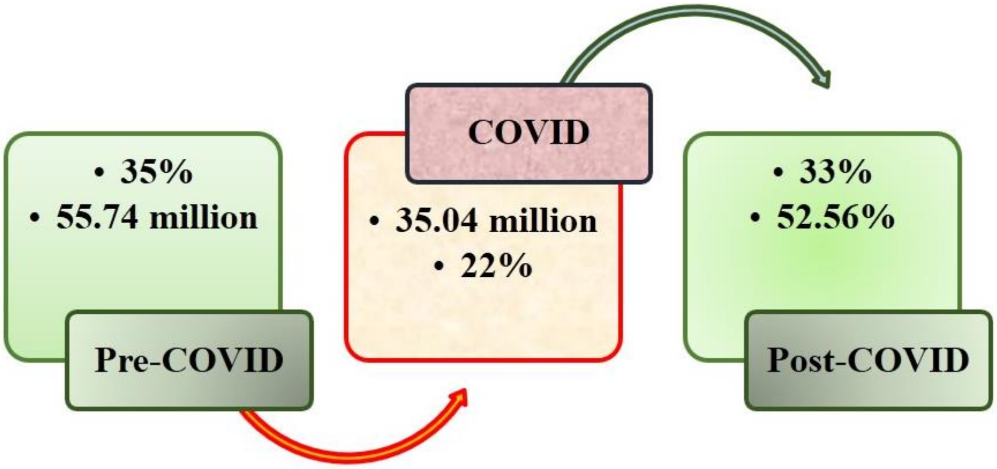

Fig. 1: Analysis of COVID-19 impact on Working Population in Pakistan

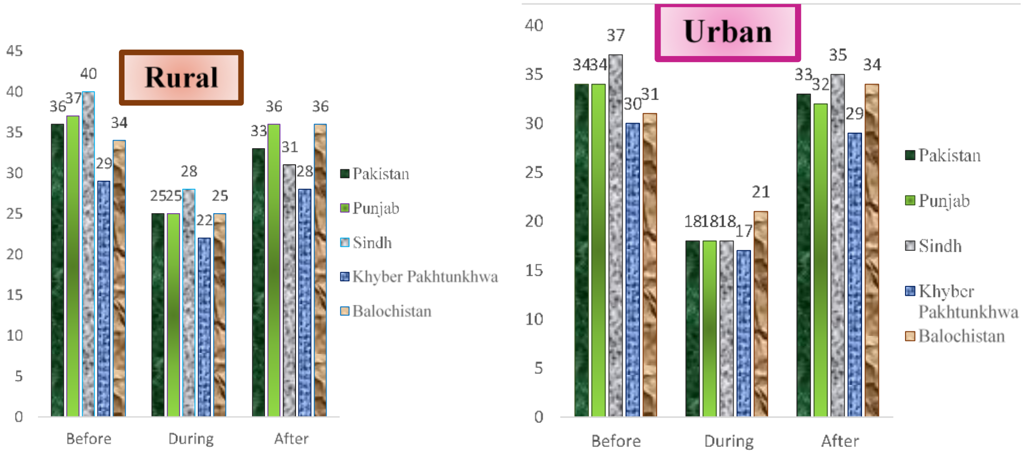

Fig. 2: Analysis of COVID-19 impact on working population in urban and rural areas of Pakistan (Pakistan Bureau of Statistics, Government of Pakistan, survey 2020)

worse as compare to the disaster in 2008 (UNCTAD 2020a). Moreover, based on International Labor Organization (ILO), 25 million individuals might have lost their jobs globally (ILO 2020c).

Currently ILO report exhibits that lockdown measures are influencing 81% of workers worldwide (ILO 2020b). Since the Second World War, this was the worst global disaster (ILO 2020b). It had been analyzed that US citizens had lost 3 million jobs during May-September in 2020 and the tendency will be comparable in European and other regions throughout the world (Siddiqui 2020). It had been estimated that the effect of COVID-19 on the economic outcome of accommodation and food services, wholesale, real estate and retail trade of motorcycles were excessive, however utilities, social work activities, public administration and defense, human health and education were also decreased (ILO 2020b). In developing countries COVID-19 will have high impact, and in under developed countries it will be more challenging for Government to implement active stimulus without facing binding foreign interchange limitations (UNCTAD 2020a). Highly susceptible regions in several countries were those that were having inferior health infrastructure, highly reliant on tourism and trade sector, highly indebted and also dependent on unsteady capital flows (Word Bank 2020a). By monitoring the COVID-19 worse impacts it was expected that economy will be recover later, however, the threats of constant financial stresses were high even after 2020 (World Bank 2020a). Additionally, it had also been assessed that scarcity was enhancing as nearly 11 million people were severely affected (World Bank 2020a). While the consequences of COVID-19 pandemic were persistent and was progressively impulsive, it was understood that the condition in developing economies would get severe prior to get improved (UNCTAD 2020a). Based on the United National Development Programme (UNDP), income losses in emerging countries were mainly to be exceeded 220billion $ (UNDP 2020b). Additionally, World Bank in its current report had expected that South Asia might challenge with inferior economic performance during last 40 years along with 50% of the countries falling into a severe downturn (World Bank 2020b).

Table 1: In Pakistan magnitude of domestic and external shock in 2019-2020 and 2020-2021

	2019-2020	2020-2021
Domestic		
Reduce in the accessibility of domestically produced Goods	-10	-5
Reduce in the accessibility of imported Goods	-15	-5
External		
Volume of World Trade	-30	-15
Unit $ Value of Import	-30	-20
Unit $ Value of Export	-20	-10
Remittances	-15	-10
From March-June 2020		

In Pakistan projected growth rate (%) in 2020 and 2021

Year	Pakistan Economy	World Economy
2020	-4.8	-3.0
2021	2.6	5.8

IMF, UNDP Macroeconomic Model

Impact of COVID-19 on Pakistan Economy and MSMEs

It had been recognized that Pakistan had lost 1/3rd of its income and foreign trades fallen by 50% due to the COVID-19 pandemic and strict lockdown (Junaidi 2020).

Researchers notify downturn of economy in Pakistan during virus lockdown (Naqvi 2020). Likewise, the World Bank also informed that Pakistan might be falling into a decline (World Bank 2020b). Due to the constant disaster of COVID-19 pandemic, Pakistan's actual GDP growth rate in FY20 was estimated to diminish nearly 1.32%, along with sharp decline in global as well as national economy during last few months of fiscal year (World Bank 2020b). Additionally, COVID-19 outbreak deteriorate and endures slower than estimated as Pakistan actual GDP growth rate in COVID-19 during fiscal year 2020 was reduced by 2.2% and earlier during FY21 just improving of 0.3% growth rate (World Bank 2020b). Table 1 enlisted the magnitude of domestic and external shocks in Pakistan during 2019-2020 and 2020-21.

Major and most instant effect of the lockdown was the stoppage of industrial processes. Lockdown was firstly declared in Sindh province during 23rd March, 2020. Karachi as the capital city of Sindh province was reflected as the main industrial zone and account for about 30% of total interchanges. However due to the lockdown, in Karachi out of total 2700 factories only 55 were working on the first working day (Hussain 2020). Moreover, it had been stated that only 5 million people in Pakistan who live just at or below survival line, however, there were masses of largely unskilled people i.e. labors, waste cycler, transport worker, construction worker and domestic worker, who work in several industries, agriculture services, and rely on daily wages to meet their requirements. It had also been analyzed that in Karachi nearly 4.1 million people were working on daily paid basis (DPB), and about 4 million peoples were working on DPB in the Punjab province. Such daily paid workers were extremely affected by lockdown. After that, micro enterprises i.e. household business, small shop owner, and street venders are highly depend on their micro business. Such business are typically run by whole members of family in several industries i.e. from agriculture to education. Moreover, such micro enterprises were measured as a part of informal economy and mostly their contribution was not well-known. It had been analyzed that micro enterprises were accounted approximately 35.7% during 2017-18 of total nationwide employment (Sohail 2019). Moreover, during 2019, nearly 55.6% of such businesses were susceptible, out of which >87% of work was in agriculture, 3/4th of the jobs were in retail trade and whole sale, approximately 50% of worker in restaurants, 3/4th of jobs in business and in real estate, and >2/5th of workers in communication and transport were susceptible (Sohail 2019).

Several small and medium sized enterprises were challenging the enormous concerns. Such as, the textile and garment industry had been affected predominantly due to the imposition of lockdown. 54% of Pakistan's industrial sector exports food i.e. tobacco, beverages and textile, and a decline in export demand for such sectors will have an inconsistent impact on Pakistan economy (World Bank 2020b). Similarly, agriculture sector had no concession. For example, harvesting of wheat crop typically begin in Sindh and southern Punjab province during March to June. Due to the stoppage of transport and un-availability of labor this sector faced numerous problems. Likely, in case of transport business, several drivers of local transportation along with buses, rickshaws and taxi drivers had been gone to home. The cessation of business and interference of national supply chain were having the marked effect on the wholesale and retail, warehouse, transport and communication facilities (World Bank 2020b). Similarly, the condition of other businesses was not varied. Most significantly, during Ramadan, several sectors i.e. saloon, clothing, electronic, food and shoes etc were rigorously impaired. Such small and medium businesses were estimated to face liquidity problems and severely affected by constant disaster. Moreover, those companies which were still functional faced extra challenges to buy masks, sanitizers and gloves etc in term of handling the health and protection of workers. Moreover, during COVID-

19, currency of Pakistan had been diminished that poses another risk for the industries. Based on current report of World Bank, foreign exchange rate of Pakistan that remained comparatively stable from June 2020-February 2021 had been devalued by 7.32% in March (World Bank 2020b).

Based on Pakistan Labor Force Survey during 2017-2018, the unemployment ratio in the country was 5.81% (Sohail 2018). While, due to constant disaster and lockdown, the unemployment rate was estimated to be reached nearly 8.12% during the fiscal year 2010-2021. The nation is currently facing numerous difficulties that were twisted with each other, including a medical crisis, economic uncertainty and uneven commodity prices. In 2020 World Economic position has expected global growth fall to 3%. From January 2020, there had been a marked decline of 6.3%. Due to the COVID-19 outbreak and lockdown, Pakistan had lost 1/3rd of its income, and exports declined by 50%. In Pakistan, economists inform to downturn of economy due to lockdown. Similarly, the World Bank also informs that Pakistan could fall into a worse downturn. Due to the current disaster produced through the COVID-19 pandemic, Pakistan's GDP growth rate in FY20 was estimated to be diminish approximately 1.32%, as the global and national action go-slow sharply during the last few months of the financial year (Siddiqui 2020). The above conversation designates that Pakistan’s economy would suffer extremely. The effects of coronavirus on worldwide and Pakistan economy will leave significant marks. However, it was tremendously significant to empirically evaluate the effects of COVID-19 pandemic on MSMEs to support policymakers and consultants to update their schemes and to support such industries survived from such constant disaster. Fig. 3 and Fig. 4 highlights the decrease in household income in different provinces of Pakistan due to COVID-19 pandemic.

Public Health Concern

The COVID-19 virus is spread by respiratory secretions of infected individuals to oral and respiratory mucous membrane cells. Coronavirus has the single stranded RNA genome enfolded in nucleocapsid protein and 3 primary proteins present on surface. COVID-19 virus is enveloped, having membrane and spike that replicate and reach the lower airways and possibly lead to severe pneumonia (Funk et al. 2020). The local spread of corona virus was estimated to be 92%. The stress of continuous staying on housebound was also lead to effect on the mental health of families. While ease in lockdown and opening of shops and markets had enhanced the transmission up to 10-fold, and according to pandemic experts, COVID-19 will keep on transmitting for the next 18-24 months until 60-70% of the community has been infected. With hospitals overload and a large number of patients and deaths, Pakistan's health scheme was trying to overcome an improbable shock (Funk et al. 2020).

COVID-19 pandemic claims intrapersonal behavior alteration and found very complex challenges for public health. An airborne infection i.e., COVID-19, transmission occurs easily by social contact, assails human relationship through significantly alter the ways by which humans interrelate. Vaccine programmes were being rolled out in different countries throughout the world which might afford by peoples, while the novel and highly transmissible variants of the virus were also being exposed. The retrieval journey looked long, with sustained interruption to social interactions. The social cost of coronavirus infection was just began to arise, while the mental health effect was already significant (Bambra et al. 2020; Pierce et al. 2020). Information of COVID-19 epidemiology accumulated rapidly, while indication of most effective policy response remained tentative. The terminology of social isolation rapidly became embedded both in public and policy dissertation. The equivalence of physical distance with social distance was undesirable, since only physical vicinity led to viral spread, while several forms of social closeness such as conversation while walking outdoor were at minimal threat, and were essential to sustain relationship helpful for health and well-being of humans (Long et al. 2022).

The arrival of COVID-19 carried the global health emergency led to the transmission of coronavirus infection having impacts on under developed countries and developed nations globally (Silva et al. 2020; Azomahou et al. 2021). The global economic disaster has antagonistic impacts on individual’s quality and mental health (Mann et al. 2020; Mtimet et al. 2021). The coronavirus pandemic was firstly appeared in Wuhan (Hubei region, China), and in this region first patient was reported on 31th December, 2019. The epidemic of COVID-19 has led to worldwide health emergency. The pandemic of coronavirus infection had affected nearly 220 territories, countries and regions along with 174.116 million infection, 3.75 million death and 157.157 million positive patients recovered from this deadly infection, as of 7th June, 2021. The arrival of COVID-19 pandemic had also immensely harmed the Pakistan’s economy (Shafi et al. 2020; Tisdell 2020; Abdullah et al. 2021).

The COVID-19 infection symptoms differ, however, normally start from fever (Islam et al. 2021), cough, headache (Islam et al. 2020), breathing difficulties, tiredness, loss of taste and sense of smell (Oran and Topol 2021; Saniasiaya et al. 2021). The occurrence of this infection may appear from day 1-14 or more after the exposure to contaminated environment or individual. Investigation showed that 35% of infected individuals don’t exhibit prominent symptoms (Nejhaddadgar et al. 2020; Shuja et al. 2020; Oran and Topol 2021). Individuals with visible infectious symptoms are considered as the actual patients (Yoosefi Lebni et al. 2021). Over 81% people showed visible mild to moderate health problems i.e., pneumonia and 14% COVID-19 infected individuals showed various sign and symptoms such as dyspnea and hypoxia. Additionally, 55 individuals showed acute symptoms of coronavirus that lead to shock, respiratory failure and other health problems i.e., multiorgan dysfunction. It has been analyzed that persons having weak

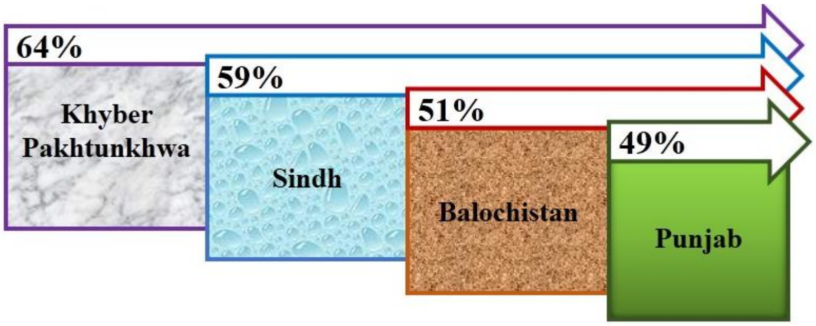

Fig. 3: % Decrease in household income in each province

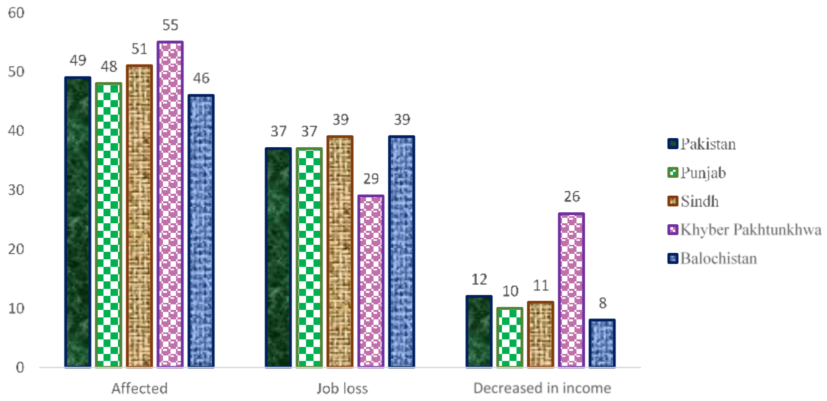

Fig. 4: Incidence of job loss in working population and decrease in income in Pakistan during COVID-19 (Government of Pakistan, survey 2020)

immune system i.e. older people facing higher threat of COVID-19 attack and lead to acute symptoms. Some infected individuals have also faced numerous health problems for months after effective retrieval from this COVID-19 infection (Shuja et al. 2020).

Future Way-out

Effective management of COVID-19 pandemic recognized that economic as well as social and health distress were complexly interlinked. It's clearly known that future inquiry and policy consideration should emphasize on the community consequence. Policies should be made by involving the communities in order to restrict the transmission of virus. Costs and their inadequate effect must not be overlooked in short term efforts to prevent an outbreak. Few public health responses such as limitation on transnational holidays travel and well-organized test and trace systems have moderately small interactive costs and must be prioritized (Long et al. 2022).

Conclusion

The COVID-19 pandemic was an extraordinary global phenomenon. It was revealed by Pakistan labor force survey conducted during 2017-2018 that unemployment rate in the country was 5.8%. While due to current disaster and lockdown, the frequency of jobless people was suspected to be enhanced up to 8.1% during financial year 2020-2021. The above debate shows that Pakistan would suffer extensively. The effects of COVID-19 on Pakistan, as well as the global economy will leave deep scars. COVID-19 transmission was very fast across the globe. According to WHO, COVID-19 cases had been reported from 206 countries with terrible deaths of >4000 individuals. The prime focus was essentially on control, cure the ill person and supporting the communities to cope with the outbreak. Our descriptive scenario designates that excessive loss of income in affected countries might be substantial along with worldwide GDP decreasing up to 4% and developing countries affected badly. Government will require to give significant funds for supporting the affected businesses and households. It is tremendously important to evaluate the effects of the COVID-19 outbreak on micro, small, medium-sized enterprises (MSMEs) to support policymakers and practitioners for streamlining their strategies to assist these businesses and to survive the current disaster.

REFERENCES

Abdullah M et al., 2021. Measuring changes in travel behavior pattern due to COVID-19 in a developing country: a case study of Pakistan. Transport Policy 108: 21-33.

ADB, 2020. Asian development outlook: What drives innovation in Asia? Special topic: The impact of the coronavirus outbreak- An update. Manila, Philippines: Asian Development Bank.

Azomahou TT et al., 2021. Coping with a dual shock: the economic effects of COVID-19 and oil price crises on African economies. Resources Policy 72: 1-12.

Bambra C et al., 2020. The COVID- 19 pandemic and health inequalities. Journal of Epidemiology and Community Health 74: 964-968.

Bartik A et al., 2020. How are small businesses adjusting to COVID-19? Early evidence from a survey. Harvard Business School Working Paper 20: 1-37.

Funk CD et al., 2020. A snapshot of the global race for vaccines targeting SARS-CoV-2 and the COVID-19 pandemic. Frontiers in Pharmacology 11: 1-17.

Hussain K, 2020. The coronavirus economy. DAWN, 29 Mar, 2020.

ILO, 2020b. COVID-19 and the world of work: Updated estimates and analysis. ILO Monitor, 2nd Ed., International Labour Organization.

ILO, 2020c. COVID-19: Protecting workers in the workplace. International Labour Organization.

Islam MA et al., 2020. Prevalence of headache in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of 14,275 patients. Frontiers in Neurology 11: 1-9.

Islam MA et al., 2021. Prevalence and characteristics of fever in adult and paediatric patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of 17515 patients. PLoS ONE 16: 1-21.

Junaidi I, 2020. Pakistan virus cases cross 5,000 mark. DAWN.

Long E et al., 2022. COVID-19 pandemic and its impact on social relationships and health. Journal of Epidemiology and Community Health 76: 128-132.

Mann FD et al., 2020. Personal economic anxiety in response to COVID-19. Personality and Individual Difference 167: 1-8.

Mtimet N et al., 2021. Zoonotic diseases and the COVID-19 pandemic: economic impacts on Somaliland's livestock exports to Saudi Arabia. Global Food Security 28: 1-7.

Naqvi H, 2020. Economists warn of recession amid virus lockdowns. Available: Pakistan Today Profithttps://profit.pakistantoday.com.pk/2020/03/30/economists-warn-ofrecession-amid-virus-lockdowns/.

NeJhaddadgar N et al., 2020. Effectiveness of telephone-based screening and triage during COVID-19 outbreak in the promoted primary healthcare system: a case study in Ardabil province, Iran. Zeitschrift fur Gesundheits wissenschaften 29: 1-6.

Oran DP and Topol EJ, 2021. The proportion of SARS-CoV-2 infections that are asymptomatic. Annals of Internal Medicine 174: 655-662.

Pakistan Economic Survey, 2020-2021. Impact of COVID-19 on Socioeconomic Situation of Pakistan, Annex IV.

Pierce M et al., 2020. Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population. Lancet Psychiatry 7: 883-892.

Prasad S et al., 2015. Building disaster-resilient micro enterprises in the developing world. Disasters 39: 447-466.

Saniasiaya J et al., 2021. Prevalence of olfactory dysfunction in coronavirus disease 2019 (COVID-19): a meta-analysis of 27,492 patients. Laryngoscope 131: 865-78.

Shafi M et al., 2020. Impact of COVID-19 pandemic on micro, small, and medium-sized Enterprises operating in Pakistan. Research in Globalization 2: 1-14.

Shuja KH et al., 2020. COVID-19 pandemic and impending global mental health implications. Psychiatria Danubina 32: 32-35.

Shuja KH et al., 2020. Letter to highlight the effects of isolation on elderly during COVID-19 outbreak. International Journal of Geriatric Psychiatry 35: 1477-1478.

Siddiqui S, 2020. COVID-19 lockdown to leave people jobless, businesses closed in Pakistan. The Express Tribune.

Silva PCL et al., 2020. COVID-ABS: an agent-based model of COVID-19 epidemic to simulate health and economic effects of social distancing interventions. Chaos Soliton and Fractals 139: 1-16.

Sohail S, 2018. Labor force survey 2017-18. Islamabad: Government of Pakistan, Ministry of Statistics, Pakistan Bureau of Statistics.

Sohail S, 2019. Pakistan employment trends-2018. Islamabad, Pakistan: Pakistan Bureau of Statistics, Ministry of Statistics, Government of Pakistan.

Tisdell CA, 2020. Economic, social and political issues raised by the COVID-19 pandemic. Economic Analysis and Policy 68: 17-28.

UNCTAD, 2020a. The Covid-19 shock to developing countries: Towards a "whatever it takes" programme for the two-thirds of the world's population being left behind. United Nations Conference on Trade and Development.

UNCTAD, 2020b. Investment trends monitor: Impact of the coronavirus outbreak on global FDI. United Nations Conference on Trade and Development.

UNDP, 2020b. COVID-19: Looming crisis in developing countries threatens to devastate economies and ramp up inequality. United Nations Development Programme.

Williams S and Schaefer A, 2013. Small and medium-sized enterprises and sustainability: Managers' values and engagement with environmental and climate change issues. Business Strategy and the Environment 22: 173-186.

Word Economic, 2020. World economic prospects monthly. Economic Outlook 44: 1-33.

World Bank, 2020a. East Asia and Pacific in the time of COVID-19. East Asia and Pacific economic update (April), Washington DC, World Bank.

World Bank, 2020b. South Asia economic focus, spring 2020: The cursed blessing of public banks. Washington DC, World Bank.

Yoosefi Lebni J et al., 2021. How the COVID-19 pandemic effected economic, social, political, and cultural factors: a lesson from Iran. International Journal of Social Psychiatry 67: 298-300.

15

Bat Borne Viral Zoonosis

AUTHORS DETAIL

Ali Zohaib[1], Momina Ejaz[2], Anam Fatima[2], Saman Noor[2], Iman Fatima[2], Medhat Rehman[1] and Aneela Javed[2*]

[1]Department of Microbiology, Faculty of Veterinary and Animal Sciences, The Islamia University of Bahawalpur
[2]Department of Healthcare Biotechnology, Atta-ur-Rahman School of Applied Biosciences (ASAB), National University of Sciences and Technology (NUST), Islamabad.
*Corresponding author: javedaneela19@gmail.com

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INTRODUCTION

A novel disease is any condition which have no known treatment and the novel disease of yesterday is the endemic disease of today. An emerging infectious disease is a newly appearing infection in a population or a previously existing disease with a fast-growing incidence or geographic range (Morens et al. 2004). Over 60 years (1940-2004), a total of 330 events of emerging infectious diseases have occurred in humans (Jones et al. 2008). Approximately 60% of these events were zoonotic and more than 70% were wildlife-related (Jones et al. 2008). Bats, carnivores, rodents, ungulates, and other animal species have all been found to have novel pathogens (Woolhouse et al. 2005). The wildlife population harbors a substantial and often unrecognized reservoir of zoonotic pathogens and serves as a zoonotic reservoir from which novel pathogens continue to emerge (Chomel et al. 2007). A variety of predisposing factors contribute to the emergence of animal-related infections including international trade, travel, deforestation, agricultural development and urbanization (Fig. 1). These factors increase the contact rate between people, domestic animals, and wildlife populations and increases the likelihood of spillover events (Daszak et al. 2001).

Bats are the only aviating and the second largest mammalian order that are found worldwide, with the exception of Antarctica, the Arctic, and a few oceanic islands. (Beena et al. 2019). The past several years have seen the emergence of a number of infectious maladies and bats are now recognized to be reservoir hosts for numerous viruses that may disseminate over species barriers and harm human health worldwide (Calisher et al. 2006). Numerous zoonotic viruses that have emerged globally are enzootic in bats and occasionally transmitted to humans and livestock (Newman et al. 2011). Bats have been established as hosts for coronaviruses, paramyxoviruses, flaviviruses, and rhabdoviruses. (Beena et al. 2019). To date, several viral genomes have been identified in bats, and for many other viruses, only serological evidence is available. Certain characteristics possessed by bats make them good candidates for reservoir hosts. Long life expectancy, species diversity, long-distance flight ability, dense nesting, spatial population structure, special immunology, and usage of torpor and hibernation have all been put forward as explanations for the rising association of bats with new infectious diseases (Calisher et al. 2006; Turmelle et al. 2009). The current bat virus database from 69 nations includes more than 4100 viruses from 23 distinct viral families and 196 bat species (Letko et al. 2020).

These cross-species infections are predisposed by social or economic situations that encourage human-bat contact. There is evidence of direct transmission from bats to pigs and horses for the Nipah and Hendra viruses. Additionally, the Nipah virus has been transmitted directly between bats and humans (Luby et al. 2006; Gurley et al. 2007). In 2007, the Melaka virus was identified in a person suffering from severe respiratory disease; however, its transmission mode remains to be explored (Chua et al. 2007). Moreover, bat lyssa viruses have been found in Australia and the United Kingdom; both are considered free of terrestrial rabies (Hanna et al. 2000; Fooks et al. 2003).

Interestingly, healthy bats have been found to harbor the majority of known bat viruses. Additionally, experimental henipavirus infection in bats resulted in viral shedding. Still, they displayed no clinical symptoms comparable to those in humans or other animals (Middleton et al. 2007). This peculiar phenomenon in bats might be ascribed to pre-infection with similar non-pathogenic viruses, viral adaptation to their host species, or some specific features of the bat immunology that are yet to be described. Due to the diversity of their species and their geographic distribution, bats might be a source of many unidentified viruses (Ge et al. 2012). Bats are considered natural reservoir hosts for numerous viruses, including SARS-CoV-1 and SARS-CoV-2, Ebola, Marburg, Nipah, Menangle, rabies, Hendra, Timon, and Australian bat lyssavirus. (Hanna et al. 2000; Han et al. 2015; Lo Presti et al. 2016; Zeltina et al. 2016; Hu et al. 2017).

Factors Contributing to the Reservoir Status of Bats

Bats may benefit from certain traits that increase their competence as reservoir hosts. Characteristics like long life expectancy, species diversity, long - distance flight, dense

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Table 1: Factors influencing the bats' reservoir status

Flight locomotion	The body temperature of certain bat species increases to 40℃ during flight, abating optimal conditions for pathogen survival inside the host, restricting the spread and dissemination of infection while boosting immunological responses (O'Shea et al. 2014).
Echolocation	Echolocation signals from bat larynx produce loud noises, producing small droplets of saliva or mucus or oropharyngeal fluids, allowing viral transmission in close proximity personals (Calisher et al. 2006).
Torpor and hibernation	For viruses like rabies which have a more extended incubation period, bats serve as a maintenance reservoir by keeping the virus dormant until the next breeding season, avoiding epizootic fadeout during hibernation (George et al. 2011). Due to the viruses' molecular co-adaptations, lowering body temperature during daily torpor also encourages viral coexistence with bat hosts (Calisher et al. 2006).
Roosting Behavior	Cave-roosting behavior, governed by roost size and specie richness is a significant driver of the virus spreading in bats. It allows increased interaction between bat species, propelling the circulation and maintenance of viruses, and endorses viral host changeover (Calisher et al. 2006).
Feeding habits	Scavenging on food scraps contaminated with an infected bat's urine or saliva may expose foraging animals to viruses carried by bats (Luby et al. 2006).

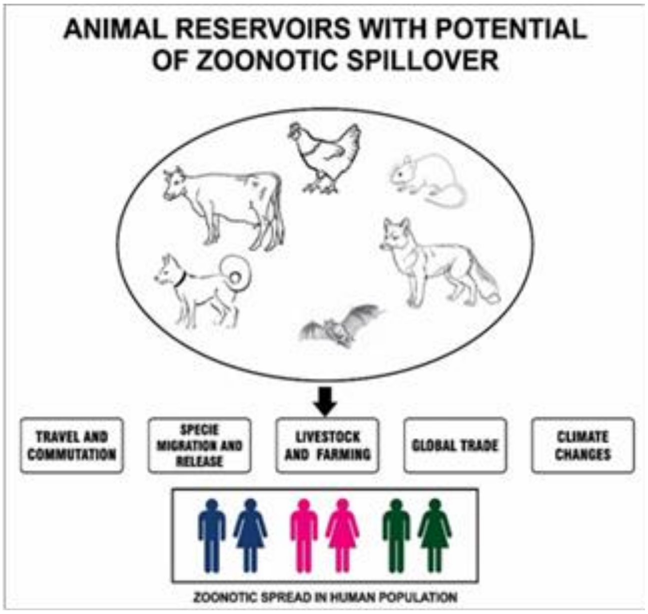
ANIMAL RESERVOIRS WITH POTENTIAL OF ZOONOTIC SPILLOVER
TRAVEL AND COMMUTATION
SPECIE MIGRATION AND RELEASE
LIVESTOCK AND FARMING
GLOBAL TRADE
CLIMATE CHANGES
ZOONOTIC SPREAD IN HUMAN POPULATION

Fig. 1: Predisposing factors contribute to the emergence of animal-related infections

perching abilities, echolocation, and usage of torpor and hibernation bracket bats and emerging infectious diseases together (Mackenzie et al. 2003). Table 1 enlisted various factors that influences the status of bat as reservoir host.

Important Emerging and Re-emerging Viruses Transmitted Through Bats

Rhabdoviridae

Bat lyssaviruses are the oldest known viruses of zoonotic origin. They are one of the most widely studied viruses in bats. Australian bat lyssavirus (ABLV) was first characterized in pteropid bats (Gould et al. 1998). A few fatal human cases have also been documented following zoonotic transmission of ABLV from Australia (Hanna et al. 2000). European Bat Lyssavirus 1 (EBLV1) has been circulating in European bats. EBLV1 has been reported in cats, sheep, and humans (Davis et al. 2005; Dacheux et al. 2009). The data regarding bat-borne Lyssaviruses from Asia is scarce. A few reports suggest the presence of bat-borne lyssa viruses from India, Siri Lanka, Thailand, and China (Lumlertdacha et al. 2005; Lu et al., 2013; Gunawardena et al., 2016; Mani et al. 2017).

Paramyxoviridae

Bats host six paramyxoviruses, including bat parainfluenza, Hendra, Mapuera, Menangle, Nipah, and Tioman viruses. In India, the first bat parainfluenza virus case from a *Rousettus leschenaulti* bat was documented in 1966 (Hollinger et al. 1971). Hendra and Nipah viruses (two of the five known Henipavirus spp.), are highly virulent bat-borne emerging viruses (Zeltina et al. 2016). Pteropus bats are considered as a reservoir host for these viruses. Pteropus bats have been routinely involved in zoonotic transmission to humans and livestock. In 1994, Hendra virus outbreaks were first reported in Australia, while Nipah virus (NiV) case was first documented in 1999 in Southeast and South Asia. During the 1999s epidemic, approximately one million pigs were diagnosed positive for NiV. The most significant cause of human infection was found to be direct contact with pigs. NiV outbreaks were reported in Bangladesh, India, Malaysia, and Singapore as well (Halpin et al. 2000; Goldspink et al. 2015; Lo Presti et al. 2016). The virus has also been reported in *Pteropus spp.*, from Cambodia, the Philippines, and Thailand (Reynes et al. 2005; Wacharapluesadee et al. 2007; Ching et al. 2015). Fig. 2 shows the transmission mode of Nipah viruses.

Fruit bats serve as natural reservoirs of Nipah viruses. Infected fruit bats visit fruit trees and feed on the fruit while naturally releasing virus-laden drops into the farm, contaminating the fruits and soil. Pigs and other animals consume tainted fruits. Pigs then act as an amplifying host as well as the intermediate host for virus transmission. Proximity to fruiting trees, animals, and humans contributes to the emergence and spread of novel lethal zoonotic viral infections such as Nipah. Pork infected with the virus is

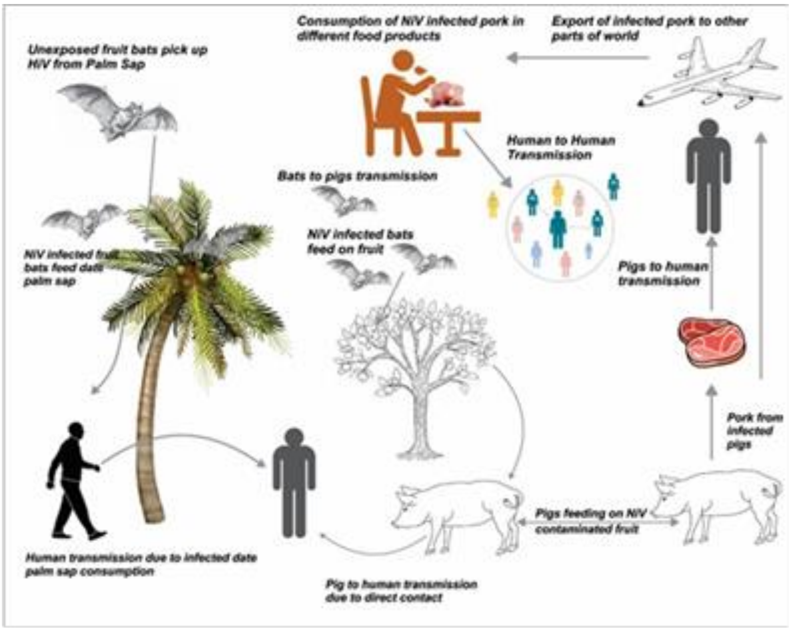
Unexposed fruit bats pick up HIV from Palm Sap
Consumption of NiV infected pork in different food products
Export of infected pork to other parts of world
Human to Human Transmission
Bats to pigs transmission
NiV infected fruit bats feed date palm sap
NiV infected bats feed on fruit
Pigs to human transmission
Pork from infected pigs
Pigs feeding on NiV contaminated fruit
Human transmission due to infected date palm sap consumption
Pig to human transmission due to direct contact

Fig. 2: Nipah virus mode of transmission.

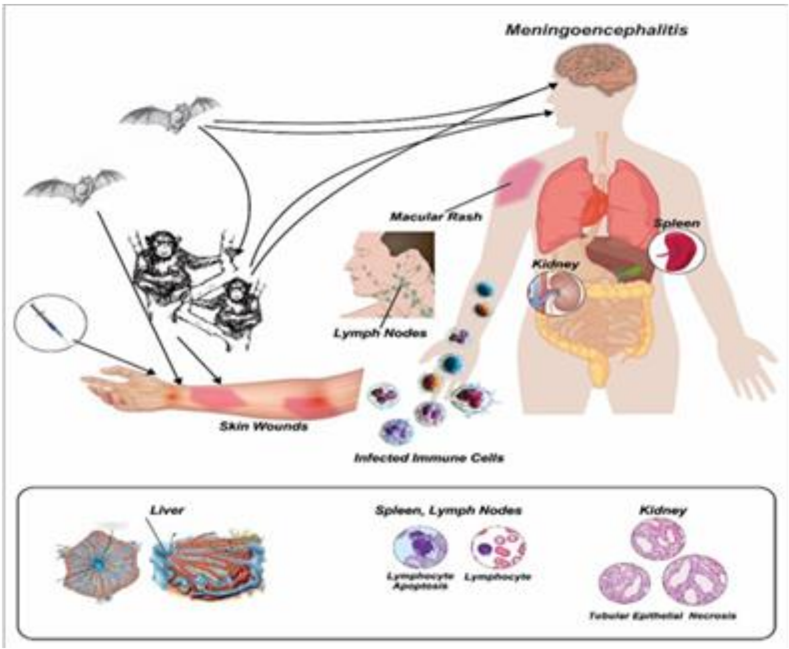

Fig. 3: Transmission and pathogenesis of Ebola virus.

exported to other countries. Humans can become ill if they consume contaminated pork. Direct contact with a Nipah virus-infected person leads to human-to-human transmission. (Ching et al. 2015).

Filoviridae

The bulk of filoviruses are single-stranded, negative sense RNA viruses. The Ebola and Marburg viruses are famous members of this family. These viruses employ bats as their natural reservoir and are linked to severe hemorrhagic disease in humans and nonhuman primates (Han et al. 2015). Reston Ebola has also been detected in pigs indicating that multiple hosts may get involved in virus circulation during human outbreaks (Marsh et al. 2011; Haddock et al. 2021). Although filovirus-associated outbreaks have only been reported from African regions, the recent studies also show the presence of Ebola Zaire and Reston viruses in Chinese and Bangladeshi bats (Yuan et al. 2012; Olival et al. 2013). Filoviruses have been found in pilipino pigs and Indonesian orangutans, demonstrating their prevalence in Asia (Marsh et al. 2011; Nidom et al. 2012). Multiple outbreaks of Ebola virus from the African continent have been reported, however disease transmission and spillover of the virus remain poorly understood (Fig. 3).

Ebola virus is spread by intimate contact with the blood, secretions, organs, or other body fluids of an infected animal. The function of infected chimpanzees, gorillas, fruit bats, and monkeys in disease transmission is crucial. Human-to-human transmission is a major risk as well. Disease symptoms include fever, muscular pain, conjunctivitis, mucosal lesions, sore throat, and unexplained bleeding and hemorrhages. (Marsh et al. 2011).

Flaviviridae

Flaviviridae, is a positive-sense single-stranded RNA virus family. Japanese encephalitis virus (JEV) and bat-derived viruses related to hepaciviruses and pegiviruses have been reported in bats (Wang et al. 2009; Quan et al. 2013). Moreover, natural infection of dengue virus (DENV) (Sotomayor-Bonilla et al. 2014), Koyose virus (YOKV) (Feng et al. 2019), Rio Bravo virus (RBV) (Price et al. 1978), Tamana bat virus (TABV) (de Lamballerie et al. 2002), and West Nile virus (WNV) has also been reported (Pilipski et al. 2004). St. Louis encephalitis virus (SLEV) has also been identified in Mexican free-tailed bats (Sulkin et al. 1966). From an epidemiological perspective, the role of bats in flavivirus transmission has not been established yet.

Coronaviridae

Coronaviruses (CoVs) belong to the *Coronaviridae* family, which are single-standard RNA viruses. The members of the subfamily Coronavirinae are spherical and comprise of Alpha, Beta, Gamma, and Delta coronaviruses (Chan et al. 2015). CoVs can infect several avian and mammalian species, including humans. Currently, seven coronaviruses have been reported to infect humans including HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43, severe respiratory syndrome coronavirus1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. HCoV-229E, HCoV-NL63, HCoV-HKU1, and HCoV-OC43 usually cause mild respiratory symptoms, whereas SARS-CoV1, MERS-CoV, and SARS-CoV-2 have significant human health threats. No case of SARS-CoV1 has been reported since 2004; nevertheless, similar viruses have been reported in bats with the ability to infect humans following a spillover event (Hu et al. 2017). Subsequent work proposes that all human coronaviruses have zoonotic origin (Fig. 4) (Corman et al. 2018).

MERS-CoV is a highly pathogenic HCoV discovered in the Kingdom of Saudi Arabia (KSA). On June 2012, an old man from KSA was admitted to Dr. Soliman Fakeeh Hospital with severe respiratory illness. The disease progressed, and the patient died after 11 days of hospitalization. The patient was detected positive for coronavirus infection. Further analysis followed, and on September 2012, Dr. Ali Moh Zaki reported the discovery of a novel HCoV (Zaki et al. 2012). It is proposed that dromedary camels serve as an intermediate host for MERS-CoV, whereas; bats serve as a reservoir host (Memish et al. 2013; Memish et al. 2014). A similar mechanism of transmission for HCoV-229E has been proposed (Corman et al. 2016). Although data suggest that bat acts as a reservoir host for HCoV-NL63 (Corman et al. 2018), however; to fully comprehend the bat-to-human spillover, further research is required. The World Health Organization (WHO) has proclaimed the coronavirus disease (COVID-19) pandemic as of March 11, 2020. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19. High sequence similarity between SARS-CoV-2 and bat coronaviruses like BANAL-52 and RaTG13 indicates a potential zoonotic spillover. (Zhou et al. 2020; Temmam et al. 2022). It was suggested that SARS-CoV-2 may have originated from bats. Other animal species, such as pangolin, were also suggested as potential intermediate hosts (Fig. 5); however, more research is needed to substantiate these theories (Zhao et al. 2020). All HCoVs mainly cause respiratory tract infection, whereas many livestock CoVs infect the gastrointestinal tract of animals. However, HCoVs can be detected in the human stool (Risku et al. 2010).

Bat Immunology

Innate Immune Responses

Receptors for conserved patterns (PRRs) that are found on pathogens are able to pinpoint certain chemical signatures (PAMPs). With virus identification these innate receptors are utilized to activate a signaling cascade, which induces cell mediators to combat the infection (Kawai et al. 2006).

Types I, II, and III interferons work actively to activate proinflammatory cytokines and interferon-stimulated genes (ISGs) (Schoggins et al. 2011). The predominant antiviral immune responses seen in bats are attributed to a contracted IFN locus that leads to a varied immune response, as seen in humans (Zhou et al. 2016). Bats display an IFNω response compared to the one elicited by IFNa in humans (Scheben et al. 2021) and IRF1 and IRF7 regulate several downstream antivirals signaling pathways (Irving et al. 2020). Unlike other animals, INFs generated by bats vary in induction and activity levels while preserving functional activity (Crameri et al. 2009; Zhou et al. 2016). Type III IFN receptors in humans vary among organs and have limited tissue distribution (Sommereyns et al. 2008). Bats have a broader range and expression, as shown in *Pteropus. alecto* (Zhou et al. 2011). Epithelial and immune cells were seen to be responsive to IFN l therapy, hinting a functional benefit of type III IFNs in *Pteropus alecto*. These findings indicate that certain bats have modified aspects of the immune responses that work to swiftly reduce a rampaging viral infection (Banerjee et al., 2020).

Furthermore, when infected with viruses such as MERS-CoV or SARS-CoV-1, bats have evolved defenses to minimize overstimulation of inflammatory reactions. These viruses,

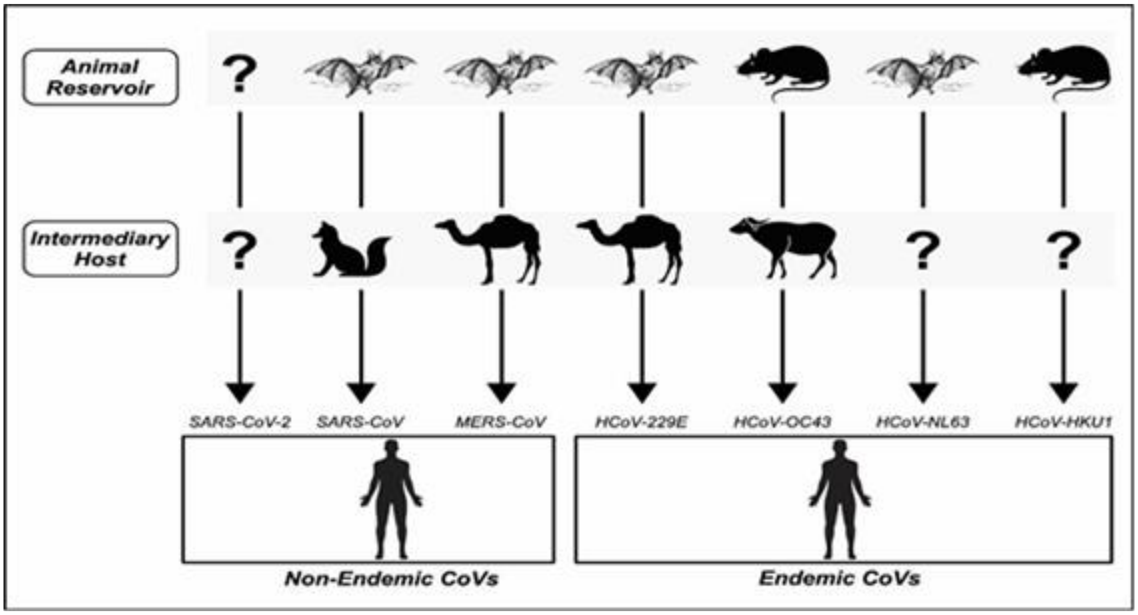

Fig. 4: Possible origin of zoonotically important coronaviruses.

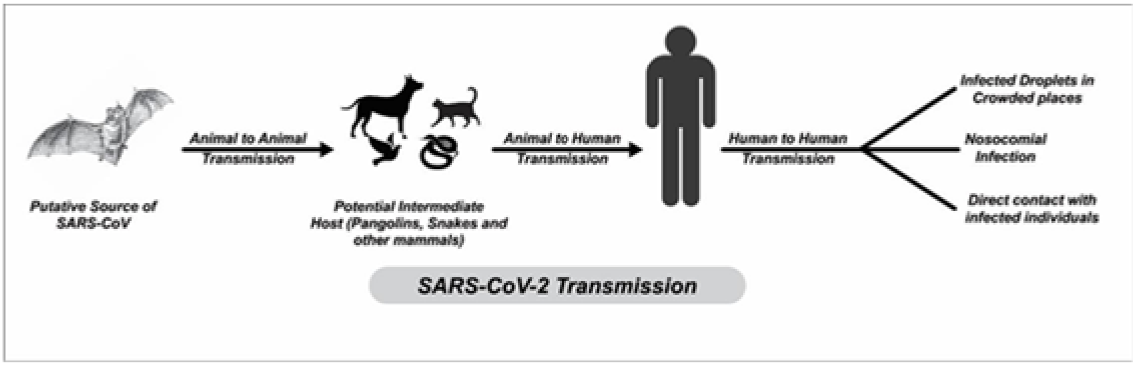
Putative Source of SARS-CoV
Animal to Animal Transmission
Potential Intermediate Host (Pangolins, Snakes and other mammals)
Animal to Human Transmission
Human to Human Transmission
Infected Droplets in Crowded places
Nosocomial Infection
Direct contact with infected individuals
SARS-CoV-2 Transmission

Fig. 5: Possible reservoir and interspecies transmission of SARS-CoV-2.

as well as others as Melaka virus and influenza A virus, are recognized and identified by the NLR-family pyrin domain containing 3 (NLRP3), which is a type of PRP (Ahn et al. 2019; Chen et al. 2019). In bats, this PRP shows a reduced expression at the transcriptional and the translational level, attributing to a decreased transcriptional priming and impaired capability of the NLRP3 isoforms (Ahn et al. 2019). Another critical immune regulator seen in bats is AIM2. It belongs to the PYHIN gene family and works to promote caspase-1 activity, which results in the cleavage of cytokines (Goh et al. 2020). Certain bat species lack the whole PYRIN and HIN domain gene family, which has a profound impact on the inflammatory state generated by a viral infection (Ahn et al. 2016).

The reduced activity of the STING found in certain bat species is attributable to a serine residue deletion in the gene. This defect significantly impacts the gene's ability to manage inflammation, infection, and cancer (Barber 2015; Xie et al. 2018).

Adaptive Immune Responses

Bats use antibodies differently than humans to control viral infection and might not be able to defeat invading viruses solely by neutralizing antibodies (Schuh et al. 2019). Antibodies against certain bat-borne viruses are seen in convalescent serum from experimentally primed infected bats to be non-neutralizing. Additionally, bat blood and spleen contain more T cells than B cells (Periasamy et al. 2019; Schuh et al. 2019).

As compared to other mammals, the major histocompatibility complexes (MHCs) in bats can detect large protein motifs (Wynne et al. 2016). Additionally, the MHC class I protein's peptide binding domain detects a larger variety of peptides than humans and other mammals, resulting in enhanced cell-mediated immune responses (Qu et al. 2019). These characteristics of bat immune systems may have evolved as a result of bats and viruses engaging in an evolutionary arms race. (Banerjee et al. 2020).

Conclusion

The prominent significance of bats in zoonotic viral infections and the well-established human-bat interaction as a result of shifting geographical conditions and anthropological practices necessitate intensive pre-emergence research. A better understanding of the viral spectrum across multiple bat species and identifying and categorizing novel bat viruses may help in the better prevention of bat-borne infectious diseases. Thus, comprehensive bat surveillance, novel virus identification, pathogenicity estimation, and reservoir identification must be performed, along with raising public awareness against bat-borne viral diseases.

REFERENCES

Ahn M et al., 2019. Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. Nature Microbiology 4(5): 789–799.

Ahn M et al., 2016. Unique Loss of the PYHIN Gene Family in Bats Amongst Mammals: Implications for Inflammasome Sensing. Scientific Reports 6: 21722.

Banerjee A et al., 2020. Novel Insights Into Immune Systems of Bats. Frontiers in Immunology 11: 26.

Barber GN et al., 2015. STING: Infection, inflammation, and cancer. Nature Reviews Immunology 15(12): 760–770.

Beena V et al., 2019. Emerging horizon for bat borne viral zoonoses. Virus Disease 30(3): 321–328.

Calisher CH et al., 2006. Bats: Important Reservoir Hosts of Emerging Viruses. Clinical Microbiology Reviews 19(3): 531–545.

Chan JFW et al., 2015. Middle East respiratory syndrome coronavirus: Another zoonotic betacoronavirus causing SARS-like disease. Clinical Microbiology Reviews 28(2): 465–522.

Chen IY et al., 2019. Severe Acute Respiratory Syndrome Coronavirus Viroporin 3a Activates the NLRP3 Inflammasome. Frontiers in Microbiology 10.

Ching PKG et al., 2015. Outbreak of Henipavirus Infection, Philippines, 2014. Emerging Infectious Diseases 21(2): 328–331.

Chomel BB et al., 2007. Wildlife, Exotic Pets, and Emerging Zoonoses. Emerging Infectious Diseases 13(1): 6–11.

Chua KB et al., 2007 A previously unknown reovirus of bat origin is associated with an acute respiratory disease in humans. Proceedings of the National Academy of Sciences 104(27): 11424–11429.

Corman VM et al., 2016. Link of a ubiquitous human coronavirus to dromedary camels. Proceedings of the National Academy of Sciences of the United States of America 113(35): 9864–9869.

Corman VM et al., 2018. Hosts and Sources of Endemic Human Coronaviruses. Advances in Virus Research 100: 163–188.

Crameri G et al., 2009. Establishment, immortalisation and characterisation of pteropid bat cell lines. PloS One 4(12): e8266.

Dacheux L et al., 2009. European Bat Lyssavirus Transmission among Cats, Europe. Emerging Infectious Diseases 15(2): 280–284.

Daszak P et al., 2001. Anthropogenic environmental change and the emergence of infectious diseases in wildlife. Acta Tropica 78(2): 103–116.

Davis PL et al., 2005. Phylogeography, population dynamics, and molecular evolution of European bat lyssaviruses. Journal of Virology 79(16): 10487–10497.

de Lamballerie X et al., 2002. Genome sequence analysis of Tamana bat virus and its relationship with the genus Flavivirus. The Journal of General Virology 83(10): 2443–2454.

Feng Y et al., 2019. Genetic diversity of the Yokose virus, XYBX1332, isolated from bats (Myotis daubentonii) in China. Virology Journal 16(1): 8.

Fooks AR et al., 2003. Case report: Isolation of a European bat lyssavirus type 2a from a fatal human case of rabies encephalitis. Journal of Medical Virology 71(2): 281–289.

Ge X et al., 2012 Metagenomic Analysis of Viruses from Bat Fecal Samples Reveals Many Novel Viruses in Insectivorous Bats in China. Journal of Virology 86(8): 4620–4630.

George DB et al., 2011. Host and viral ecology determine bat rabies seasonality and maintenance. Proceedings of the National Academy of Sciences of the United States of America 108(25): 10208–10213.

Goh G et al., 2020. Complementary regulation of caspase-1 and IL-1β reveals additional mechanisms of dampened inflammation in bats. Proceedings of the National Academy of Sciences of the United States of America 117(46): 28939–28949.

Goldspink LK et al., 2015. Natural Hendra Virus Infection in Flying-Foxes—Tissue Tropism and Risk Factors. PloS One 10(6): e0128835.

Gould AR et al., 1998. Characterisation of a novel lyssavirus isolated from Pteropid bats in Australia. Virus Research 54(2): 165–187.

Gunawardena PS et al., 2016. Lyssavirus in Indian Flying Foxes, Sri Lanka. Emerging Infectious Diseases 22(8): 1456–1459.

Gurley ES et al., 2007. Person-to-Person Transmission of Nipah Virus in a Bangladeshi Community. Emerging Infectious Diseases 13(7): 1031–1037.

Haddock E et al., 2021. Reston virus causes severe respiratory disease in young domestic pigs. Proceedings of the National Academy of Sciences of the United States of America 118(2): e2015657118.

Halpin K et al., 2000. Isolation of Hendra virus from pteropid bats: A natural reservoir of Hendra virus. The Journal of General Virology 81(8): 1927–1932.

Han HJ et al., 2015. Bats as reservoirs of severe emerging infectious diseases. Virus Research 205: 1–6.

Hanna JN et al., 2000. Australian bat lyssavirus infection: A second human case, with a long incubation period. The Medical Journal of Australia 172(12): 597–599.

Hollinger et al., 1971. Bat parainfluenza virus. Immunological, chemical, and physical properties. The American Journal of Tropical Medicine and Hygiene 20(1): 131–138.

Hu B et al., 2017. Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS Pathogens 13(11): e1006698.

Irving AT et al., 2020. Interferon Regulatory Factors IRF1 and IRF7 Directly Regulate Gene Expression in Bats in Response to Viral Infection. Cell Reports 33(5): 108345.

Jones KE et al., 2008. Global trends in emerging infectious diseases. Nature 451(7181): 990–993.

Kawai T et al., 2006. Innate immune recognition of viral infection. Nature Immunology 7(2): 131–137.

Letko M et al., 2020. Bat-borne virus diversity, spillover and emergence. Nature Reviews Microbiology 18(8): 461–471.

Lo Presti et al., 2016. Origin and evolution of Nipah virus. Journal of Medical Virology 88(3): 380–388.

Lu ZL et al., 2013. Lyssavirus surveillance in bats of southern China's Guangxi Province. Virus Genes 46(2): 293–301.

Luby S et al., 2006. Foodborne Transmission of Nipah Virus, Bangladesh. Emerging Infectious Diseases 12(12): 1888–1894.

Lumlertdacha B et al., 2005. Bat lyssavirus in Thailand. Journal of the Medical Association of Thailand 88(7): 1011–1014.

Mackenzie JS et al., 2003. Managing emerging diseases borne by fruit bats (flying foxes), with particular reference to henipaviruses and Australian bat lyssavirus. Journal of Applied Microbiology 94: 59-69.

Mani RS et al., 2017 Serological Evidence of Lyssavirus Infection among Bats in Nagaland, a North-Eastern State in India. Epidemiology and Infection 145(8): 1635–1641.

Marsh GA et al., 2011. Ebola Reston Virus Infection of Pigs: Clinical Significance and Transmission Potential. The Journal of Infectious Diseases 204(3): 804–809.

Memish ZA et al., 2014. Human infection with MERS coronavirus after exposure to infected camels, Saudi Arabia, 2013. Emerging Infectious Diseases 20(6): 1012–1015.

Memish ZA et al., 2013. Middle East Respiratory Syndrome Coronavirus in Bats, Saudi Arabia. Emerging Infectious Diseases 19(11): 1819–1823.

Middleton DJ et al., 2007. Experimental Nipah Virus Infection in Pteropid Bats (Pteropus poliocephalus). Journal of Comparative Pathology 136(4): 266–272.

Morens DM et al., 2004. The challenge of emerging and re-emerging infectious diseases. Nature 430(6996): 242–249.

Newman SH et al., 2011. Investigating the Role of Bats in Emerging Zoonoses: Balancing Ecology, Conservation and Public Health Interest, FAO.

Nidom CA et al., 2012. Serological evidence of Ebola virus infection in Indonesian orangutans. PloS One 7(7): e40740.

Olival KJ et al., 2013. Ebola Virus Antibodies in Fruit Bats, Bangladesh. Emerging Infectious Diseases 19(2): 270–273.

O'Shea TJ et al., 2014. Bat Flight and Zoonotic Viruses. Emerging Infectious Diseases 20(5): 741–745.

Periasamy P et al., 2019. Studies on B Cells in the Fruit-Eating Black Flying Fox (Pteropus alecto). Frontiers in Immunology 10.

Pilipski JD et al., 2004. West nile virus antibodies in bats from New Jersey and New York. Journal of Wildlife Diseases 40: 335-337.

Price JL et al., 1978. Isolation of Rio Bravo and a hitherto undescribed agent, Tamana bat virus, from insectivorous bats in Trinidad, with serological evidence of infection in bats and man. The American Journal of Tropical Medicine and Hygiene 27(1): 153–161.

Qu Z et al., 2019. Structure and Peptidome of the Bat MHC Class I Molecule Reveal a Novel Mechanism Leading to High-Affinity Peptide Binding. Journal of Immunology 202(12): 3493–3506.

Quan PL et al., 2013. Bats are a major natural reservoir for hepaciviruses and pegiviruses. Proceedings of the National Academy of Sciences 110(20): 8194–8199.

Reynes JM et al., 2005. Nipah Virus in Lyle's Flying Foxes, Cambodia. Emerging Infectious Diseases 11(7): 1042–1047.

Risku M et al., 2010. Detection of human coronaviruses in children with acute gastroenteritis. Journal of Clinical Virology: The Official Publication of the Pan American Society for Clinical Virology 48(1): 27–30.

Scheben A et al., 2021. Long-read sequencing reveals rapid evolution of immunity- and cancer-related genes in bats.

Schoggins JW et al., 2011. Interferon-stimulated genes and their antiviral effector functions. Current Opinion in Virology 1(6): 519–525.

Schuh AJ et al., 2019. Antibody-Mediated Virus Neutralization Is Not a Universal Mechanism of Marburg, Ebola, or Sosuga Virus Clearance in Egyptian Rousette Bats. The Journal of Infectious Diseases 219(11): 1716–1721.

Sommereyns C et al., 2008. IFN-lambda (IFN-lambda) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. PLoS Pathogens 4(3): e1000017.

Sotomayor-Bonilla J et al., 2014. Dengue Virus in Bats from Southeastern Mexico. The American Journal of Tropical Medicine and Hygiene 91(1): 129–131.

Sulkin SE et al., 1996. Isolation of St. Louis encephalitis virus from bats (Tadarida b. Mexicana) in Texas. Science 152(3719): 223–225.

Temmam S et al., 2022. Bat coronaviruses related to SARS-CoV-2 and infectious for human cells. Nature 604(7905): 330–336.

Turmelle AS et al., 2009. Correlates of Viral Richness in Bats (Order Chiroptera). EcoHealth 6(4): 522–539.

Wacharapluesadee S et al., 2007. Duplex nested RT-PCR for detection of Nipah virus RNA from urine specimens of bats. Journal of Virological Methods 141(1): 97–101.

Wang JL et al., 2009. Japanese Encephalitis Viruses from Bats in Yunnan, China. Emerging Infectious Diseases 15(6); 939–942.

Woolhouse MEJ et al., 2005 Host Range and Emerging and Reemerging Pathogens. Emerging Infectious Diseases 11(12): 1842–1847.

Wynne JW et al., 2016. Characterization of the Antigen Processing Machinery and Endogenous Peptide Presentation of a Bat MHC Class I Molecule. Journal of Immunology 196(11): 4468–4476.

Xie J et al., 2018. Dampened STING-Dependent Interferon Activation in Bats. Cell Host and Microbe 23(3): 297-301.

Yuan J et al., 2012. Serological evidence of ebolavirus infection in bats, China. Virology Journal 9: 236.

Zaki AM et al., 2012. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. The New England Journal of Medicine 367(19): 1814–1820.

Zeltina A et al., 2016. Emerging Paramyxoviruses: Receptor Tropism and Zoonotic Potential. PLoS Pathogens 12(2): e1005390.

Zhao J et al., 2020. The Potential Intermediate Hosts for SARS-CoV-2. Frontiers in Microbiology 11.

Zhou P et al., 2011. Type III IFN receptor expression and functional characterisation in the pteropid bat, Pteropus alecto. PloS One 6(9): e25385.

Zhou P et al., 2016. Contraction of the type I IFN locus and unusual constitutive expression of IFN-α in bats. Proceedings of the National Academy of Sciences of the United States of America 113(10): 2696–2701.

Zhou P et al., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579(7798): 270–273

16

Rotavirus Gastroenteritis: A Food-borne Viral Disease

AUTHORS DETAIL

Waqar Zaib[1], Kashif Hussain[1], Qurratulain Amin[2], Rana Muhammad Shahbakht[1], Asghar Abbas[1], Safder Imran[3], Rabeea Sardar[4], Muhammad Umair Waqas[1], Muhammad Asif Raza[1], Junaid Ali Khan[1], Hafeez Ur Rehman Ali Khera[1] and Shahwaiz Tariq[1]

[1]Faculty of Veterinary and Animal Sciences, Muhammad Nawaz Shareef University of Agriculture, Multan 66000, Pakistan
[2]Riphah College of Veterinary Sciences, Lahore 55150, Pakistan.
[3]Faculty of Veterinary and Animal Sciences, The Islamia University of Bahawalpur 63100, Pakistan.
[4]Department of Biotechnology, The Women University Multan 66000, Pakistan
*Corresponding author: waqar.zaib@mnsuam.edu.pk

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INTRODUCTION

The world has witnessed a series of new virulent virus outbreaks in recent years due to contaminated food consumption like SARS coronavirus, monkeypox virus, avian influenza virus, and Nipah Virus. These outbreaks are usually associated with the specific food habit of a particular region but worldwide consequences have made us more concerned about the possibility of transmission of emerging viruses to humans via consumption of contaminated food during processing (Troeger et al. 2017). The burden of foodborne viruses is not completely calculated yet but according to an estimate WHO (2015) suggested that 15% and 23.6% of foodborne diarrheal deaths were attributed to the invasion by norovirus and hepatitis A virus respectively (Menon et al. 2016). Besides these, other viruses like enteroviruses, sapoviruses, rotaviruses, astroviruses, and adenoviruses have also been implicated in food (NAAS 2020). Along with other viruses, rotavirus is the leading cause of severe diarrhea in children in developed and developing countries accounting for about 22% of the global deaths caused by this virus (Tate et al. 2016). Rotavirus is highly contagious and mostly spreads through the fecal-oral route. Although the burden of rotavirus illness has been extensively mapped, however little attention has been paid to identifying other potential modes of transmission (Kotwal et al. 2014).

The landscape of rotavirus (RV) infection has changed substantially and it's much broader than diarrhea and autoimmune triggering has covered the clinical spectrum of its pathology. The host genetic background in RV susceptibility has provided vaccine effectiveness and added to the limited efficacy of RV vaccines in underdeveloped settings. The intestinal and extraintestinal microbiota impact of RV infection and their widening clinical picture has promised mechanisms of host susceptibility and vaccine efficacy. RV infection is a systemic disease with clinical and pathophysiological implications beyond the gut. The "iceberg" model has covered the pathology of hidden clinical implications which lead to the triggering of autoimmune disease other than gastrointestinal infection (Gómez-Rial et al. 2019).

The surveillance of circulating rotaviruses in the human population has confirmed the uncommon strains that are usually found in domestic companion animals and livestock and genome studies of these is also required, besides rotavirus A (João et al. 2020).

Genetic Diversity of Rotavirus

The rotavirus belongs to the *Reoviridae* family and Genus *Rotavirus* is divided into nine different virus species which can rapidly mutate due to genome reassortment resulting in new strains. The rotavirus genus has nine species; A, B, C, D, E, F, G, H, I and J (Leung et al. 2005). Specie A, B and C mostly infect human and species A to E cause disease in animals. Rotavirus has different strains defined by outer protein G and P. Rotaviruses have no envelope with three-layer capsid and double standard RNA genome. Strains of rotavirus called serotypes VP7 glycoprotein define G serotypes and VP4 defines P serotypes (Phan et al. 2016). There are around 36 G and 51 P types, respectively. There are non-structural and structural proteins which are only produced in cells infected by rotavirus (Kirkwood 2010).

Rotavirus A is the most common specie, responsible for more than 90% of infections in humans (Leung et al. 2005). According to World Health Organization, rotavirus strains show significant diversity but it has 5 major serotypes, A through E, which are responsible for the majority of rotavirus infections in humans (João et al. 2020).

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Geographical Distribution

To find the burden of disease in different geographical regions of the world different epidemiological studies are formed worldwide which shows that genotypes including G1P, G3P, G4P, G2P and G9P have caused severe disease mostly in children during last 20 years (Gentsch et al. 2005). Among all genotypes, G1P is most common around 70% in countries like USA and UK and around 20 to 25 % in less developed areas like south America and Africa (Ward 1996). Rotavirus vaccines are specifically effective against rotavirus types G1, G2, G3, G4, and G9, because they are most common in causing diseases. G6, G8, and G10 cause disease mostly in the bovines (Cunliffe et al. 2001). G5 is most common in Brazil and G10 is common in Indian children (Banerjee et al. 2006). The highest rate was reported in Bangladesh, Vietnam, Thailand, and South Korea, respectively. The highest proportions were in Southeast Asia around 37.5% in hospitalized gastroenteritis cases. Rotavirus causes 147,000 deaths per year in Asia, with the highest numbers occurring in Pakistan, India, and Indonesia. In short, rotavirus causes hospitalization and deaths among children thorough out Asia and cause large healthcare expenditures (Kawai Kosuke et al. 2012).

In Pakistan, the relative prevalence and mortality rate due to rotavirus is 67.6 per 1,00,000 children (Sadiq et al. 2019).

The prevalence of rotavirus group A (RVA) after the introduction of vaccines against rotavirus in fecal samples, subjected to Enzyme Linked Immunosorbent Assay (ELISA) technique and reverse transcriptase PCR (RT-PCR) shows 22% and 21% prevalence of rotavirus in children with acute gastroenteritis, respectively (Basharat et al. 2021). Fig. 1 shows the death rate caused by rotavirus across the world.

Transmission of Rotavirus in Humans

Rotavirus is highly contagious and mainly transmitted via the fecal-oral route through ingestion of contaminated food and water, or by person-to-person contact. It has a short incubation period of 1-2 days. Rotaviruses are zoonotic viruses causing nosocomial diarrhea (Dennehy et al. 1990) and has been associated with gastroenteritis outbreaks in the daycare setting (O'Ryan et al. 1990).

In humans, transmission occurs mainly by fecal-oral route (Butz et al. 1993). Rotavirus can be spread through stool-contaminated objects (toys, door-handlers, faucets, or toilet seats), contaminated food and water, or airborne droplets (Fig. 2). Fecal-oral transmission is common in daycare centers and family homes which is facilitated by intimate and frequent exposure among vulnerable hosts (Keswick et al. 1983).

Infants become infected by touching contaminated toys and putting fingers in their mouths. Healthcare providers can also spread the virus due to improper hand-washing after changing diapers. Diaper changing is the highest risk procedure for rotavirus transmission. Therefore, proper hand-washing and good hygiene are important to control the spread of rotaviral infections (Doro et al. 2015).

Rotavirus infects children less than 3 years and can be passed from infected children to others who are in close contact. It is one of the leading causes of dehydrating diarrhea among children around the globe with an estimated more than 2 million pediatric admissions and 25 million cases in outpatient clinics every year (Parashar et al. 2003).

The rotavirus enters through the mouth and then infects the gastrointestinal lining. Infected children shed a large amount of rotavirus in their stool and the virus gets into the environment and infects other people. Shedding can occur 48 hours before the onset of symptoms and continue until 21 days after infection (Pickering et al. 1988). Presymptomatic shedding and the high rate of asymptomatic infections are significant factors for rotavirus transmission (Parashar et al. 2003).

The shedding of rotaviruses occurs in very high concentrations. Infected infants excrete 100 billion particles per gram of stool (Flewett 1983) whereas asymptomatic people shed intermittently or lower quantities of virus. Asymptomatic carriers are common. The infectious dose of rotavirus is relatively small as 10-100 virus particles are sufficient to cause infection in susceptible individuals (Estes et al. 2013). These viruses are very stable as they can survive for several days on objects, remain infective on hands for a minimum of 4 hours and survive for weeks in drinking or recreational water (Kapikian et al. 1983). There is adequate proof that it is a waterborne pathogen. Rotavirus can retain its infectivity for a long time in an aqueous environment. The waterborne spread has been implicated in various outbreaks, although there isn't sufficient proof that water alone is responsible for its transmission (Doro et al. 2015).

Rotavirus infections are more common in winter and spring. It has been known as ‘winter diarrhea’ in some countries. Children are at high risk during these seasons. Any child who is in close contact with an infected or material object, is at risk of being infected (Dey et al. 2010).

Pathogenesis of Rotavirus Gastroenteritis

Recent research has revealed several mechanisms of Rotavirus gastroenteritis which are quite complex than previously appreciated. There occurs a complex interaction of host associated factors with viral proteins. The early events in rotavirus gastroenteritis are mediated by interaction of intestinal epithelial cells and viral antigens (Estes et al. 2001). There are four mechanisms involved in inducing gastroenteritis:

(1). Occurrence of malabsorption followed by the destruction of intestinal cells. (Estes et al. 1995).

(2). Destabilization of cell permeability due to virus encoded non-structural protein 4, also known as rotavirus enterotoxin which is a transmembrane glycoprotein. This enterotoxin has a potential role in inducing diarrhea by disrupting the ion balance inside the enterocytes. It increases the intracellular concentration of Ca ions by mobilizing these from endoplasmic reticulum (Estes et al. 1995).

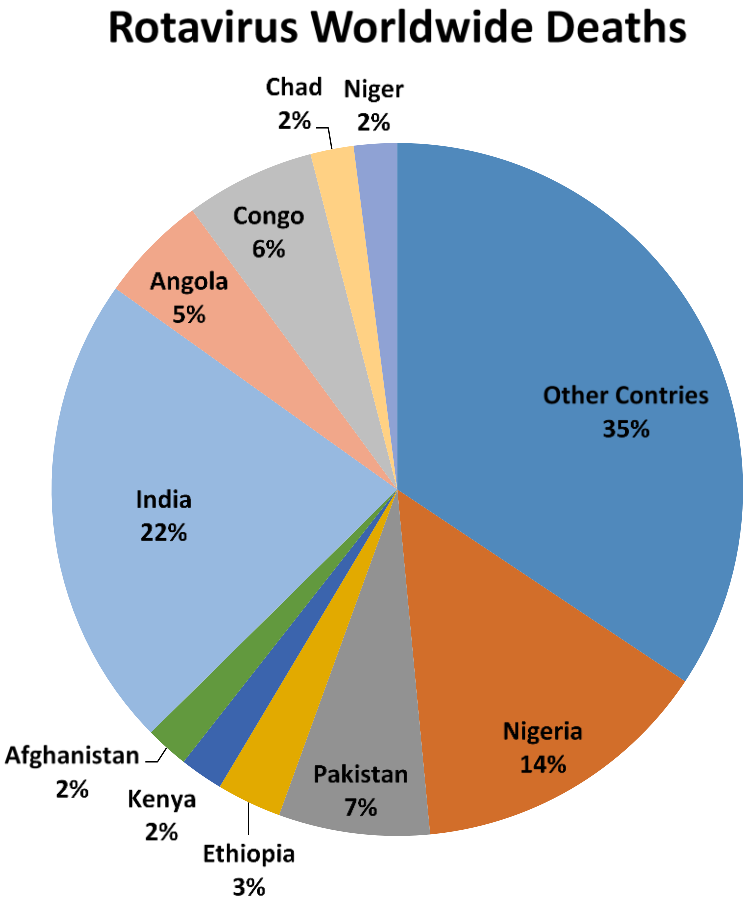

Fig. 1: Death's caused by rotavirus across the world

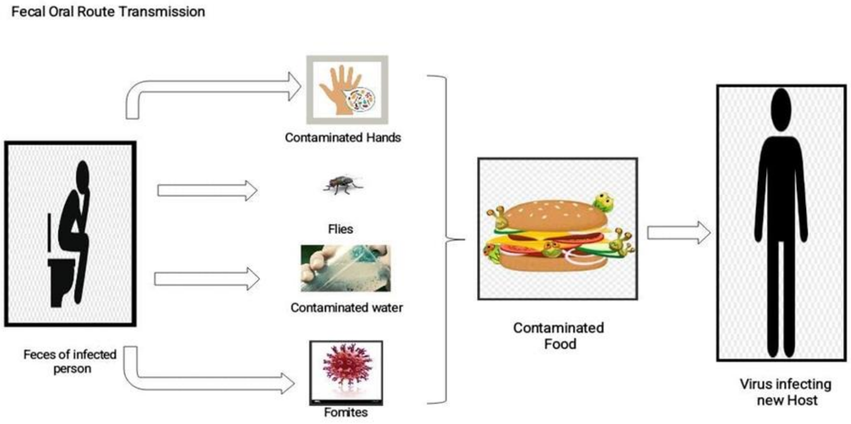

Fig. 2: Transmission of Rotavirus

(3). Development of ischemia in villi and enteric nervous system activation, possibly evoked by vasoactive agents released from damaged epithelial cells (Ramig 2004).

(4) Further, NSP-4 destabilizes the permeability of the plasma membrane and facilitates the leakage of lactate dehydrogenase from the cells (Tian et al. 1996; Lundgren and Svensson 2001).

After ingestion through contaminated feed and water, rotavirus reaches the intestine and infects the enterocytes. It replicates in non-dividing and mature enterocytes in the tip and middle of the villi (Dennehy 2008) and also in endocrine cells of small intestine (Shakya et al. 2022). The attachment to the host cell is mediated by viral capsid protein-4 with its VP-8 domain present on the host cell surface (Shakya et al.

2022). After successful entry into the enterocytes virus starts producing its progeny in upper small intestine and damages the intestinal villi, resulting in reduced surface area leading towards malabsorption. The imbalanced ions concentration inside the cell mediated via enterotoxin activate the intestinal secretions (Shakya et al. 2022). Infectious viral particles, some of which are osmotically active are also drained inside the intestinal lumen which further impairs the reabsorption of water from large intestine resulting in very profuse watery diarrhea. Along with this, the absorption of mucosal disaccharides, water and sodium ions is also decreased whereas levels of cAMP remain unchanged. A transition of undigested and unabsorbed carbohydrates, fats, and proteins is produced in intestinal lumen that further disseminates osmotic diarrhea (Ramig 2004). The lack of oxygen supply towards epithelial cells also contributes to diarrhea (Osborne et al. 1988). The pathophysiology of rotavirus gastroenteritis is still an area of intense research. The research findings show no visible lesions of hemorrhages in the intestine but slight changes at cellular levels i.e., loss of villi, blunting of villi, enterocyte vacuolization, and hyperplasia of intestinal crypts (Osborne et al. 1988).

Clinical Features

The incubation period is variable between 1 to 3 days (Schweitzer et al. 2016). 48–78% of rotavirus infections are usually asymptomatic in neonates (Huggins 1942). Studies have revealed that recovery after infection at early stages can confer immunity for infection in later stages of life (Ramani et al. 2008). The most pronounce clinical signs include vomiting, pyrexia, and fever. The signs start with vomiting followed by mild diarrhea which later can become severe along with recurrent vomiting and high fever. Pyrexia is not a common sign in rotavirus gastroenteritis and is seen in 33% of infected patients only (Shakya et al. 2022). Besides these signs, physical examination of the infected patients also reveals signs of dehydration i.e., tachycardia, prolonged capillary refill, dry mucous membranes, reduced skin turgor, and decreased urine output (Hoxha et al. 2015). The clinical signs are variable among full term and premature babies. The full-term babies manifest the symptoms as described earlier, whereas premature neonates are shown to have feeding difficulties, lethargy, and abdominal distention (Shim et al. 2012). The manifestation of clinical signs also depends on whether it is the recurrent infection or first infection. The susceptible patients show more severe clinical picture if infection occurs after 3 months of age. In rare cases, necrotizing enterocolitis has also been observed in infants (Schweitzer et al. 2016). The differential diagnosis is vital to rotavirus gastroenteritis as symptoms are usually like other enteric infections, but the symptoms tend to be more severe in rotavirus infection. However, clinical diagnosis based upon signs and symptoms is difficult until or unless it is also supported with some laboratory evidence. Most of the patients recover within 5 to 7 days after infection (Shim et al. 2012).

Complications

Prolonged course of infection can lead to the onset of many complicated conditions in patients. Persistent diarrhea and vomiting can result in severe water loss from body (Belhorn 1999). The nature of dehydration is mostly isotonic (Belhorn 1999; Lee et al. 2003). Besides this, the occurrence of hypernatremic dehydration (too much water loss and imbalance of salts, too much sodium gain in patient's body) is greater than expected (Kovacs et al. 1987; Ho and Bradford 1995). Disaccharidase deficiency can also occur due to persistent and prolonged diarrhea. The concurrent infection of upper and lower respiratory tract has also been reported along with rotavirus infection (Karampatsas et al. 2018). Further, the concurrent rotavirus infection can occur with Reye's syndrome (Ioi et al. 2006), pancreatitis (Giordano et al. 2013), intussusception (McGeoch et al. 2020), hepatic abscess (Leung et al. 2005), meningoencephalitis (Leung et al. 2005), seizures (Lloyd et al. 2010), Kawasaki's disease (D'Auria et al. 2009), encephalitis (Kawamura et al. 2014), enterocolitis, myositis (BONNO et al. 1998), and poliomyelitis like syndrome (Leung et al. 2005). Generalize systemic infection can also occur due to dissemination of rotavirus from GIT (Dalgıç et al. 2010). Research has also reported the replication of rotavirus in kidney and liver cells along with enterocytes (Crawford et al. 2006).

Effect of Age on Clinical Severity

Age is an important factor that impacts the severity of disease. Premature neonates with low antibodies level, during early infancy develop very severe disease (Shakya et al. 2022). Many full-term neonates who acquire protective maternally derived antibodies during the third trimester, can tolerate the infection with very mild symptoms. As soon as the passively acquired immunity starts to get fade, the infants can again become susceptible to rotavirus infection at the age of 6 months to 3 years. Recovered infants develop neutralizing antibodies (IgG, and IgA), which confers protection from subsequent recurrent infection (Franco 2006).

Diagnosis

Latex agglutination (LA), enzyme-linked immunosorbent assay (ELISA), polyacrylamide gel electrophoresis (PAGE), and enzyme immunoassay (EIA) can be used for the detection and diagnosis of the Rotavirus infection. While latex agglutination (LA) shows more specificity, sensitivity and predictive value against RV infections and can be done in low-income settings as well. RT-PCR also give highest sensitivity and specificity for laboratory findings of RV infection, but it costs high. In routine laboratory use, LA and ELISA based kits are preferred (El-Ageery et al. 2017; Hamzavi et al. 2017).

Treatment

No specific antiviral serum therapy is offered yet for RV infections. The use of probiotics has been adjuncted along with the rehydration therapy in routine (Dennehy 2013). Treatment of acute rotavirus infection is nonspecific and involves control of symptoms and, most importantly, control of dehydration (Diggle 2007). If untreated, children can die from severe dehydration (Alam and Ashraf 2003). Depending on the severity of diarrhea, treatment consists of oral rehydration therapy, during which the child is given excess water to drink that contains specific quantities of salt and sugar (Sachdev 1996). In 2004, World Health Organization (WHO) and UNICEF recommended the use of low-osmolarity oral rehydration solution and zinc supplementation as a two-pronged treatment of acute diarrhea. Some infections are serious enough to warrant hospitalization where fluids are given by intravenous therapy or nasogastric intubation, and the child's electrolytes and blood sugar are watched (Patel et al. 2007). Rotavirus infections infrequently cause other complications and for a well-managed child the prognosis is excellent (Ramig 2007). Probiotics have been shown to reduce the duration of rotavirus diarrhea (Ahmadi et al. 2015).

Rotavirus Vaccine

The Centers for Disease Control and Prevention recommends that vaccination is the most effective way to control rotavirus transmission and protect children from rotavirus diarrhea. In developing countries, the rotavirus vaccines prevent 15–34% of severe infections and 37–96% of infections in developed countries (Bergman et al. 2021). These vaccines provide good protection against rotavirus infection. It decreases the death risk among infants and reduces the number of infections among adults and non-vaccinated people (Patel et al. 2011).

There are currently two licensed oral vaccines for rotavirus in the United States:

- RotaTeq® (RV5) is given in 3 doses at the age of 2 months, 4 months, and 6 months
- Rotarix® (RV1) is given in 2 doses at the age of 2 months and 4 months

The WHO recommends that the first dose of the rotavirus vaccine should be given after the age of 6 weeks monovalent vaccine (RV1; Rotarix, GlaxoSmithKline). Infants should get fully vaccinated before they become 8 months old. A few drops (1.5ml) of vaccine are poured into the mouth with the dropper (Bergman et al. 2021).

The rotavirus vaccine is very effective as it has significantly reduced the severity and the incidence rate of rotavirus disease (Giaquinto et al. 2011). Moreover, these vaccines prevent infections in non-vaccinated infants by limiting exposure to already circulating rotavirus infections (Patel et al. 2011). The WHO released statistics for the period 2000–2013, showing significant decreases in mortality rates and hospital admissions due to rotavirus diarrhea in developing countries after the introduction of the vaccination programs (Parashar et al. 2016).

Rota Council shared that more than 100 countries have granted licenses for rotavirus vaccines, and over 80 countries have made its vaccination a common practice. The likelihood of serious side effects is extremely small. The rotavirus vaccines are considered safe, but some infants may become irritable and restless or may develop mild diarrhea. Rotavirus vaccine may rarely cause a severe allergic reaction or intussusception (Bergman et al. 2021).

Preventive Strategies and Approaches

The implementation and monitoring of the standard operating procedure during food processing and handling should be ensured at the food industry (WHO 2015). Farm to fork approach should be adopted by multi-disciplinary teamwork involving veterinarians, microbiologists, environmentalists, industry, and most importantly consumers. The disease burden clearly states that enforcement of food safety system should be followed in both developed and low-income settings to avoid the outbreaks of RV infection (Tate et al. 2016).

Conclusion

Acute diarrhea is one of the most important causes of morbidity and mortality in young children. Rotavirus is the major pathogen causing diarrhea worldwide and especially found in developing countries. It results in many hospitalization costs, and deaths. Rotavirus infection is the leading cause of severe dehydrating gastroenteritis in children under 5 years of age. Despite the global introduction of the rotavirus vaccine over a decade ago, this disease still kills more than 200,000 people annually, mostly in low-income countries. Reinfection with rotavirus is common throughout life, but repeated infections reduce disease severity. Although the immune correlates of protection from rotavirus reinfection and recovery are poorly understood, rotavirus-specific immunoglobulin A plays a role in both aspects. Treatment of rotavirus infection focuses on preventing and treating dehydration but may require the use of antiviral and antiemetic drugs.

REFERENCES

Ahmadi E et al., 2015. Efficacy of probiotic use in acute rotavirus diarrhea in children: A systematic review and meta-analysis. Caspian Journal of Internal Medicine 6: 187–195.

Alam NH and Ashraf H, 2003. Treatment of infectious diarrhea in children. Paediatric Drugs 5: 151–165.

Banerjee et al., 2006. Comparative study of the epidemiology of rotavirus in children from a community-based birth cohort and a hospital in South India. Journal of Clinical Microbiology 44: 2468-2474.

Basharat N et al., 2021. Rotavirus gastroenteritis in Pakistan, 2018: updated disease burden. BMC Infectious Diseases 21: 1-6.

Belhorn T, 1999. Rotavirus diarrhea. Current Problems in Pediatrics 29: 198-207.

Bergman H et al., 2021. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 11.

Bishop RF, 1996. Natural history of human rotavirus infection. Viral Gastroenteritis 1996: 119-128.

BONNO M et al., 1998. Acute myositis with transient decrease of albumin, immunoglobulin, and complement following rotavirus gastroenteritis. Pediatrics International 40: 82-84.

Bostan N et al., 2019. Molecular characterization of human group A rotavirus genotypes circulating in Rawalpindi, Islamabad, Pakistan during 2015-2016. PloS one 14 : e0220387.

Butz AM et al., 1993. Prevalence of rotavirus on high-risk fomites in day-care facilities. Pediatrics 92: 202–205.

Crawford SE et al., 2006. Rotavirus viremia and extraintestinal viral infection in the neonatal rat model. Journal of Virology 80: 4820-4832.

Cunliffe NA et al., 1997.Rotavirus strain diversity in Blantyre, Malawi, from 1997 to 1999. Journal of Clinical Microbiology 39: 836-843.

D'Auria E et al., 2009. A case of Kawasaki disease with anasarca and concomitant rotavirus infection. Case Reports 2009: 1020081092.

Dalgıç N et al., 2010. Is rotavirus diarrhea a systemic viral infection?. Journal of Pediatric Infection/Cocuk Enfeksiyon Dergis 4.

Dennehy PH and Peter G, 1985. Risk factors associated with nosocomial rotavirus infection. American Journal of Diseases of Children 139: 935–939.

Dennehy PH, 2000. Transmission of rotavirus and other enteric pathogens in the home. Pediatric Infectious Disease Journal 19: 103–5.

Dennehy PH, 2008. Rotavirus vaccines: an overview. Clinical Microbiology Reviews 21: 198-208.

Dennehy PH, 2013. Treatment and prevention of rotavirus infection in children. Current Infectious Disease Reports 15: 242-50.

Dey SK et al., 2010. Seasonal trend and serotype distribution of rotavirus infection in Japan, 1981–2008. The Pediatric Infectious Disease Journal 29: 166-167.

Diggle L, 2007. Rotavirus diarrhea and future prospects for prevention. British Journal of Nursing 16: 970–974.

Doro R et al., 2015. Zoonotic transmission of rotavirus: surveillance and control. Expert Review of Anti-infective Therapy 13: 1337-1350.

El-Ageery SM et al., 2020. Comparison of enzyme immunoassay, latex agglutination and polyacrylamide gel electrophoresis for diagnosis of rotavirus in children. Egyptian Journal of Basic and Applied Sciences 7: 47-52.

Estes MK et al., 2001. Pathogenesis of rotavirus gastroenteritis. In: Chadwick DJ, Goode JA, editors. Gastroenteritis Viruses: Novartis Foundation Symposium; pp: 82-100.

Estes MK et al., 2013. Rotaviruses In: Kinpe DM, Howley PM, editors. Fields virology sixth edition Philadelphia: Lippincott; pp: 347-401.

Evan J Anderson and Stephen G Weber, 2004. Rotavirus infection in adults. The Lancet Infectious Diseases 4: 91-99.

Flewett TH, 1983. Rotavirus in the home and hospital nursery. British Medical Journal Clinical Research 287: 568.

Fragoso M et al., 1986. Rotavirus in nasopharyngeal secretions of children with upper respiratory tract infections. Diagnostic Microbiology and Infectious Disease 4: 87-88.

Franco MA, 2006. Immunity and correlates of protection for rotavirus vaccines. Vaccine 24: 2718-2731.

Gallimore CI, 2005. Detection of multiple enteric virus strains within a foodborne outbreak of gastroenteritis: an indication of the source of contamination. Epidemiology and Infection 133: 41-47.

Gentsch JR et al., 2005. Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine programs. Journal of Infectious Diseases 192: 146-159.

Giaquinto C et al., 2011. Summary of effectiveness and impact of rotavirus vaccination with the oral pentavalent rotavirus vaccine: a systematic review of the experience in industrialized countries. Human Vaccines 7: 734-748.

Giordano S et al., 2013. Acute pancreatitis in children and rotavirus infection. Description of a case and minireview. New Microbiologica 36: 97-101.

Gleizes O et al., 2006. Nosocomial rotavirus infection in European countries: a review of the epidemiology, severity and economic burden of hospital-acquired rotavirus disease. The Pediatric Infectious Disease Journal 25: 12-21.

Gómez-Rial et al., 2019. Rotavirus infection beyond the gut. Infection and Drug Resistance 12: 55.

Grimwood K and Lambert SB, 2009. Rotavirus vaccines: opportunities and challenges. Human Vaccines 5: 57–69.

Hamzavi H et al., 2018. Performance of Latex agglutination, ELISA and RT-PCR for diagnosis of Rotavirus infection. Journal of Biological Research - Bollettino Della Società Italiana Di Biologia Sperimentale 90.

Ho L and Bradford BJ, 1995. Hypernatremic dehydration and rotavirus enteritis. Clinical Pediatrics 34(8): 440-441.

Hoxha T et al., 2015. Performance of clinical signs in the diagnosis of dehydration in children with acute gastroenteritis. Medical Archives 69: 10.

Huggins C, 1942. Effect of orchiectomy and irradiation on cancer of the prostate. Annals of Surgery 115: 1192.

Ioi H et al., 2006. A case of Reye syndrome with rotavirus infection accompanied with high cytokines. Journal of Infection 52: e124-e128.

João ED et al., 2020. Molecular epidemiology of rotavirus a strains pre-and post-vaccine (Rotarix®) introduction in Mozambique, 2012–2019: emergence of genotypes G3P[4] and G3P[8]. Pathogens 9: 1–16.

Julian TR., 2016. Environmental transmission of diarrheal pathogens in low and middle income countries. Environmental Science: Processes and Impacts 18: 944-955.

Kapikian AZ et al., 1983. Oral administration of human rotavirus to volunteers: induction of illness and correlates of resistance. Journal of Infectious Diseases 147: 95-106.

Karampatsas K et al., 2018. Clinical characteristics and complications of rotavirus gastroenteritis in children in east London: A retrospective case-control study. PloS one 13: e0194009.

Kawai Kosuke et al., 2012. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. Vaccine 30: 1244-1254.

Kawamura Y et al., 2014. Nationwide survey of rotavirus-associated encephalopathy and sudden unexpected death in Japan. Brain and Development 36: 601-607.

Keswick BH et al., 1983. Survival and detection of rotaviruses on environmental surfaces in day care centers. Applied and Environmental Microbiology 46: 813-816.

Kirkwood CD, 2010. Genetic and antigenic diversity of human rotaviruses: potential impact on vaccination programs. Journal of Infectious Diseases 202: S43-S48.

Kotwal A et al., 2014. A study of Hepatitis A and E virus seropositivity profile amongst young healthy adults in India. Medical Journal Armed Forces India 70: 225-229.

Kotwal G and Cannon JL, 2014. Environmental persistence and transfer of enteric viruses. Current Opinion in Virology 4:.37-43.

Kovacs A et al., 1987. Rotavirus gastroenteritis: clinical and laboratory features and use of the Rotazyme test. American Journal of Diseases of Children 141: 161-166.

Lee WS et al., 2003. Hospitalization of childhood rotavirus infection from Kuala Lumpur, Malaysia. Journal of Paediatrics and Child Health 39(7): 518-522.

Leung AK et al., 2005. Rotavirus gastroenteritis. Advances in Therapy 22: 476-487.

Lloyd et al., 2010. Rotavirus gastroenteritis and seizures in young children. Pediatric Neurology 42: 404-408.

Lundgren O and Svensson L, 2001. Pathogenesis of rotavirus diarrhea. Microbes and Infection 3: 1145-1156.

McGeoch et al., 2020. Impact of rotavirus vaccination on intussusception hospital admissions in England. Vaccine 38: 5618-5626.

Menon et al., 2016. Norovirus gastroenteritis in a birth cohort in Southern India. PLoS One 11: 0157007.

Mukhopadhya I et al., 2017. Changing molecular epidemiology of rotavirus infection after introduction of monovalent rotavirus vaccination in Scotland. Vaccine, 35: 156-163.

NAAS, 2020. Food-borne Zoonotic Diseases, Policy Paper No. 95, National Academy of Agricultural Sciences, New Delhi.

O'Ryan ML et al., 1990. Molecular epidemiology of rotavirus in children attending day care centers in Houston. Journal of Infectious Diseases 162: 810-816.

Osborne MP et al., 1988. An electron microscopic investigation of time-related changes in the intestine of neonatal mice infected with murine rotavirus. Journal of Pediatric Gastroenterology and Nutrition 7: 236-248.

Parashar UD et al., 2003. Global illness and deaths caused by rotavirus disease in children. Emerging Infectious Diseases 9: 565.

Parashar UD et al., 2016. Health impact of rotavirus vaccination in developing countries: progress and way forward. Clinical Infectious Diseases 62: 91-95.

Patel MM et al., 2007. Routine laboratory testing data for surveillance of rotavirus hospitalizations to evaluate the impact of vaccination. The Pediatric Infectious Disease Journal. 26: 914–919.

Patel MM et al., 2011. Real-world impact of rotavirus vaccination. The Pediatric Infectious Disease Journal 30: 1-5.

Phan MV et al., 2016. Unbiased whole-genome deep sequencing of human and porcine stool samples reveals circulation of multiple groups of rotaviruses and a putative zoonotic infection. Virus Evolution 2: 27.

Pickering LK et al., 1988. Asymptomatic excretion of rotavirus before and after rotavirus diarrhea in children in day care centers. The Journal of Pediatrics 112: 361-365.

Prince DS et al., 1986. Aerosol transmission of experimental rotavirus infection. Pediatric Infectious Disease 5: 218-222.

Ramani S et al., 2008. Rotavirus infection in the neonatal nurseries of a tertiary care hospital in India. The Pediatric Infectious Disease Journal 27(8): 719-723.

Ramig RF, 2007. Systemic rotavirus infection. Expert Review of Anti-infective Therapy 5: 591–612.

Ramig RF, 2004. Pathogenesis of intestinal and systemic rotavirus infection. Journal of Virology 78: 10213-10220.

Rao VC et al., 1984. Isolation of enteroviruses from water, suspended solids, and sediments from Galveston Bay: survival of poliovirus and rotavirus adsorbed to sediments. Applied and Environmental Microbiology 48: 404-409.

Rheingans R et al., 2018. Effects of geographic and economic heterogeneity on the burden of rotavirus diarrhea and the impact and cost-effectiveness of vaccination in Pakistan. Vaccine 36: 7780-7789.

Rotavirus Deaths and Rotavirus Vaccine Introduction Maps—ROTA Council". Rotacouncil.org. Archived from the original on 2016-07-12. Retrieved 2016-07-29

Sachdev HP, 1996. Oral rehydration therapy. Journal of the Indian Medical Association 94: 298–305.

Sadiq A et al., 2019. Molecular characterization of human group A rotavirus genotypes circulating in Rawalpindi, Islamabad, Pakistan during 2015-2016. PloS one 14: e0220387.

Schweitzer A et al., 2016. Impact of rotavirus vaccination on coverage and timing of pentavalent vaccination–Experience from 2 Latin American countries. Human Vaccines and Immunotherapeutics 12: 1250-1256.

Shakya P et al., 2022. Rotavirus Infection in Neonates and Young Infants.

Shim JO et al., 2012. Clinical characteristics and genotypes of rotaviruses in a neonatal intensive care unit. Pediatrics and Neonatology 53(1): 18-23.

Simpson DL and Brooks CL, 1999. Tailoring the structural integrity process to meet the challenges of aging aircraft. International Journal of Fatigue 21: 1-14.

Tate JE et al., 2016. World Health Organization–Coordinated Global, Rotavirus Surveillance Network, Global, regional, and national estimates of rotavirus mortality in children< 5 years of age, 2000–2013. Clinical Infectious Diseases 62: 96-105.

Tian P et al., 1995. The rotavirus nonstructural glycoprotein NSP4 mobilizes Ca2+ from the endoplasmic reticulum. Journal of Virology 69(9): 5763-5772.

Tian P et al., 1996. The rotavirus nonstructural glycoprotein NSP4 possesses membrane destabilization activity. Journal of Virology 70(10): 6973-6981.

Troeger C et al., 2017. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrheal diseases: A systematic analysis for the Global Burden of Disease Study 2015. The Lancet Infectious Diseases 17: 909-948.

Ward RL, 1996. Mechanisms of protection against rotavirus in humans and mice. Journal of Infectious Diseases 174: 51-58.

World Health Organization, 2014 Estimated rotavirus deaths for children under 5 years of age: 2013, 215 000. WHO. Archived from the original on April 2, 2014. Retrieved 2021-03-30.

World Health Organization, 2013. Rotavirus vaccines: WHO position paper—January 2013. Weekly Epidemiological Record Relevé épidémiologique hebdomadaire 88: 49-64.

17

Rabies: The Vet-verse of Madness

AUTHORS DETAIL

Tayyaba Ameer[1]*, Shamreza Aziz[1], Irza[2], Muhammad Younus[3], Qamar un Nisa[4], Tayyaba Akhtar[1], Waqas Ahmad[5], Muhammad Ifham Naeem[1] and Saim Shahbaz[1]

[1]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[2]Department of Epidemiology & Public Health, University of Veterinary and Animal Sciences-Lahore.
[3]Department of Pathobiology, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[4]Department of Pathology, University of Veterinary and Animal Sciences-Lahore.
[5]Department of Clinical Sciences, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
*Corresponding author: tayybaawan678@gmail.com

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INTRODUCTION

Rabies, the Latin verb "rabere" means "to be mad." Rabies is an ancient viral zoonotic disease with a high case fatality rate. More than 75% of infectious diseases that are newly emerging and 60% of infectious diseases that are known to affect humans are spread by animals. Due to its high mortality rate, rabies is the zoonoses with the greatest public health concern (Acharya et al. 2021).

It is caused by an RNA virus acting on the central nervous system of its host, causing degenerative changes in the brain and spinal cord, leading to the death of the infected animal or person due to encephalitis. The rabies virus (RABV) is thought to be contagious in all mammals. It has a nearly 100% case fatality rate (Fooks et al. 2014).

Rabies is endemic everywhere except for islands like Australia and Antarctica. While over 15 million people follow rabies post-exposure vaccinations annually, over sixty thousand humans die of rabies annually (Wilde et al. 2013). The outbreak of rabies is controlled by extensive pre- and post-exposure prophylactic vaccination programs (Briggs 2012). Its incidence is more in developing countries due to a lack of proper vaccination and knowledge. Rabies has been declared a multi-species affecting infection by the World Health Organization (Jackson 2016). Although it is a vaccine-prevented disease, the canine rabies virus variant can produce a horrifying death after the bite of a rabid dog and thus, termed as dog-mediated rabies (Yousaf et al. 2012). The different organizations of the world are working on the slogan of 'Zero by 30' under the flag of the World Health Organization (WHO) to eradicate this deadly disease (Ridder et al. 2016).

Etiology

As the name indicates, rabies is termed as madness. In Sanskrit, the word "rabies" comes from the "rabhas," which means "to provoke violence" (Afonso et al. 2016). Instead of being a mere historical relic, terrifying myth, or literary allegory, rabies is a serious viral encephalitis with the highest case fatality rate of any common infectious disease. The rabies virus affects the central nervous system of the host producing Negri bodies in the brain causing the inflammation of the active tissues of the spinal cord and brain leading to madness and ultimately death of the animal. The rabies virus is a member of the Mononegavirales order of neurotropic viruses, which have single negative-stranded RNA genomes that are not segmented (Madhusudana et al. 2013). The Rhabdoviridae family is categorized in this order having specific bullet-shaped viruses in it. This family contains three different genera of animal viruses, which are Lyssavirus, Vesiculovirus, and Ephemerovirus. The Lyssavirus genus contains the Rabies virus. The word Lyssa is derived from the name of the goddess in Greek "Lyssa", who represents the 11 souls of insanity, hysteria, and anger (Hankins and Rosekrans 2004). The lyssavirus has seven distinct genotypes as shown in Table 1. They are isolated from different hosts.

The genome of the rabies virus is composed of the nucleoprotein, Phospho-protein, and RNA-dependent RNA-polymerase proteins which formed a complex known as ribonucleoprotein complex primarily involved in the multiplication of the Rabies virus in the host cells' cytoplasm. The phosphorylation of the nucleoproteins is responsible for its fast multiplication (Xianfu et al. 2002). The matrix proteins present in the structure of RABV are accountable for the interaction with the trans-membranous spikes of G proteins and the budding and assembly of bullet-shaped particles (Mebatsion et al. 1999). The glycoproteins of RABV are responsible for the pathogenicity of the virus and are the only proteins exposed on the surface of the virus. The G proteins induce protective immunity against the RABV virus. On the surface of the virus, the glycoprotein produces about 400 closely packed trimeric spikes (Albertini et al. 2011; Zhu and Guo 2016).

Citation: Ameer T, Aziz S, Irza, Younus M, Nisa QU, Akhtar T, Ahmad W, Naeem MI and Shahbaz S, 2023. Rabies: The vet-verse of madness. In: Aguilar-Marcelino L, Abbas RZ, Khan A, Younus M and Saeed NM (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. I, pp: 106-115. https://doi.org/10.47278/book.oht/2023.17

Table 1: Different genotypes of lyssavirus.

No.	Genotype number	Genus Name	Origin of isolation	Date of isolation	Reference
1	Genotype 1	Rabies virus (RABV)	Isolated one strain from new world bats and the other from dogs.	1768	(Badrane and Tordo 2001).
2	Genotype 2	Lagos bat virus	Isolated from frugivorous bats	1956	(Boulger and Porterfield 1958)
3	Genotype 3	Mokola virus	Isolated from Crocidura species,	1968	(Shope et al. 1970)
4	Genotype 4	Duvenhage virus	Isolated from a human died due to a bat bite.	1970	(Meredith et al. 1971)
5	Genotype 5	European bat lyssavirus 1	Isolated from Eptesicus serotinus bats.	1968	(Schneider and Cox 1994).
6	Genotype 6	European bat lyssavirus 2	Isolate from a human in Finland and mainly present in bats of the Myotis genus.	1985	(Lumio et al. 1986).
7	Genotype 7	Australian bat lyssavirus	Isolated from one type of insectivorous bat and five species of flying fox bats.	1996	(McCall et al. 2000).

The size of the genome of Genotype 1 (RABV) is approximately 12 kb and it consists of five different types of structural proteins including (Albertini et al. 2011):

1. Nucleo-protein (N)
2. Phospho-protein (P)
3. Matrix protein (M)
4. Glycoprotein (G)

RNA-dependent RNA-polymerase protein (L)

Transmission

Lyssavirus is distributed by mammals from the Carnivora and Chiroptera orders, including bats, foxes, jackals, coyotes, skunks, raccoons, mongooses, and monkeys (Rupprecht et al. 2008). Mainly canines are responsible for the fast spread of Rabies among humans and other animals. As it is a zoonotic disease, both animals and humans are affected by this. The main source of transmission is a bite by a rabid animal, that is a dog in about 99% of cases in under-developed regions like Africa and Asia (Wunner and Briggs 2010). After entering the host body through the contact of the saliva of the infected animal with the body of the host, the virus enters the central nervous system (Jackson et al. 2013).

From CNS, it moves toward the salivary glands of the host with the help of facial and glossopharyngeal nerves. From the Salivary gland of the host, RABV is now ready to enter the new host (Jackson et al. 2013). Non-bite modes of Rabies transfer are scratches from rabid pets like cats and dogs, contact of open wounds with the saliva of rabid animals, and inhalation of the RABV virus in a large concentration (Singh et al. 2017). Dog bites carry a 5%–80% risk of rabies, which is around 50 times greater than the 0.1–1% risks faced by licks or scratches (Hemachudha et al. 2013). The incidence of non-bite rabies has been very low in the last 50 years. The bite of a Rabid human can also transfer rabies, but it is less confirmed. Only one report is available of biting a rabid human into another human (Feder et al. 2012). The transmission of the virus by the transplantation of organs is also reported. No RABV virus is isolated from feces, but the body fluids like nervous tissue fluids and tears contain the virus and can transmit the disease (Rupprecht et al. 2002). The whole Rabies cycle is controlled naturally by the sylvatic and urban cycles, and both are interconnected (Campos et al. 2002). The interlinkage of both cycles is illustrated in Fig. 1.

Pathogenesis

The Rabies virus is no doubt 100% fatal. Once the clinical signs appear then there is no way back (Fooks et al. 2014). RABV causes an illness that is fatal once it begins to show clinical signs but develops slowly. The incubation time of the disease varies from 14 days to 6 years and the appearance of clinical signs entirely depends upon the viral concentration at the inoculation or biting site (Susilawathi et al. 2012). The biting site has a complete bearing on how long the incubation period lasts. The greater the site of the bite closer to the CNS less will be the incubation period and the earlier the host starts to appear the symptoms (Hankins and Rosekrans JA 2004). More risk factors are bites on the neck, shoulder and hands and encounter of saliva with the blood of the host leads to early transfer of the virus to the brain due to encounters with more neurons. As the rabies virus has the potential to stay in the myocytes of the muscles for a longer period, this potency of RABV is helpful for the removal of the virus from those muscles by post-exposure treatment with the assistance of host immune system (Hemachudha et al. 2002).

The life cycle of a virus starts when it gets into the host body either by the bite of a rabid animal or by any other means. After entry, it gets attached to the target cells like myocytes, locally present motor, or sensory neurons through G-proteins receptors. The sites for the replication of the rabies virus are either myocytes or the macrophages of the host body. The replication in the muscle fibers is a vital infective step for the virus to enter the peripheral nervous system (Jackson 2010). Up to 18 days the rabies virus can persist and multiply there (Baer 2012). The virus then binds with the nicotinic acetylcholine receptors present at neuromuscular junctions (Lewis et al. 2000). The virus travels towards CNS along the nerves about 3 mm per hour and enters the central nervous system to infect the nerve cells by muscle spindles of sensory nerves or neuromuscular junction of motor nerves (Mazarakis et al. 2001). A rapid axonal retrograde transport

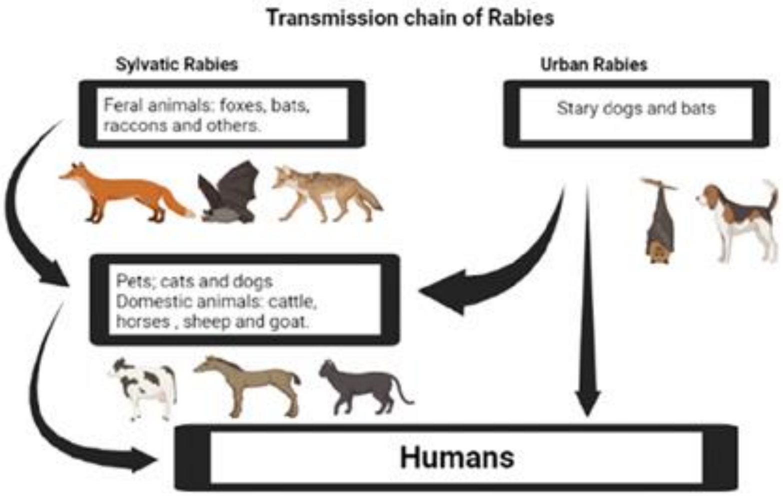
Transmission chain of Rabies
Sylvatic Rabies
Feral animals: foxes, bats, raccons and others.
Urban Rabies
Stary dogs and bats
Pets; cats and dogs
Domestic animals: cattle, horses , sheep and goat.
Humans

Fig. 1: The sylvatic and urban transmission chains of Rabies, Sylvatic mostly occurs in developed countries while Urban mostly occurs in underdeveloped countries.

mechanism that moves RABV toward the CNS at a pace of 12-100 mm per day travels across sensory and motor axons (Kelly and Strick 2000). The virus then again replicates in the motor neurons of the spinal cord and ganglia. After entering the brain, it causes the infection of the brain neurons leading to inflammation (Koyuncu et al. 2013).

For better infection and reproduction in the brain system, the neurotrophic RABV has evolved with a variety of defense mechanisms to escape the host immune system, which results in fatal encephalomyelitis (Lafon 2011). After infecting the brain, the virus enters the salivary glands and other organs like the eyes, and kidneys of the victim (Moore and McVey 2022). Typically, the sensory and autonomic innervations of skin and subcutaneous tissues are abundant, playing a role in infection brought on by deeper bites of vectors. The virus may potentially enter blood since there are big inoculums at the biting site (Singh et al. 2017). The whole pathogenesis of the rabies virus is shown in Fig. 2.

The Rabies virus is entirely host-dependent; it can't survive outside the host body. Sunlight and any harsh fluctuation in the atmosphere can lead to the death of the virus (Fekadu et al. 1988).

Clinical Signs and Symptoms

After the RABV exposure either by bite or any other route, the virus must travel and reach the central nervous system. When it grows and multiplies, the animal or human shows signs and symptoms. The incubation period for rabies is about 20 to 90 days (Jackson 2010; Hemachudha et al. 2013). The incubation period entirely depends on the immunity of the host, the virulence factor of the virus, and the distance of the biting site from the brain (Jackson 2003). The appearance of signs, symptoms, and outcomes of disease vary between animals and humans. Early symptoms are the same in both humans and animals i.e., flu including restlessness, mild fever, pain, itching at the biting site, burning sensation at the site of the wound, mild tingling, excessive salivation, and mild headache. These symptoms last for a few days (Hankins and Rosekrans 2004). Early symptoms remain for 2-5 days then progress to paralytic versions in almost 75% of the cases of dogs. 4 to 8 days after the onset of clinical symptoms, paralysis, and mortality occur. Rabies in animals is divided into two phases: the Prodromal phase and the exciting phase (Table 2).

Human rabies consists of two forms, encephalitis (furious) and dumb (paralytic) form. In both forms, the brainstem of the brain is involved (Hemachudha et al. 2002). Humans experience various signs of infection that are mentioned in Table 3.

Treatment

As Rabies is a viral-transmitted disease, it has no proper treatment. Rabies is virtually always fatal, and once central nervous system symptoms start to show, the mortality rate can exceed 100% even when pre-exposure prophylaxis is administered. Only, supportive treatment is present. The only way to prevent rabies is pre-exposure vaccination. Currently, immunoglobulins for rabies against humans and horses are available for providing passive immunity to the body (Both et al. 2012). But if the animal or human can get a bite by a rabid dog, it is necessary to care for the wound. Immediately wash the bite area with carbolic soap and water for about 10 minutes to minimize the risk of secondary bacterial infection (Balakrishnan 2018). After that, check the wound thoroughly to check for the presence of any foreign body like a broken tooth. Following this, we leave the wound to heal by the second intention as the closing of the wound increases the risk of bacterial proliferation and infection in the wound. Ready-made immunoglobulins against rabies should be administered to the patient (Daniel et al. 2004).

Table 2: Clinical signs of different phases of the Rabies virus in animals (Blanton et al. 2009)

No.	The phases of Rabies	Clinical Signs and symptoms
1	Prodromal phase	Hypersensitivity and increased response to light and noise, irritability, aggressive(cats), alertness, hiding in dark places, depression, attack without provocation, restlessness, slight pyrexia, biting site self-mutilation, and an impaired corneal reflex.
2	Excited phase	Vicious bite, attack, nervous signs like irritability, flaccidity, muscle tremors, incoordination, spasms, dysphagia, jaw-dropping, coma, paralysis, and death.

Table 3: Clinical signs of different phases of the Rabies virus in humans (Nigg and Walker 2009)

No.	The phases of Rabies	Clinical signs
1	Furious form	Burning sensation at the biting site, itching, hyperactivity, gastrointestinal tract distress, hyperactivity, hallucinations, excitable behavior, hydrophobia, and aerophobia.
2	Paralytic form	Paralysis of muscles starting from the biting site and then paralysis of the eyes, tongue, and lungs leading to coma and death.

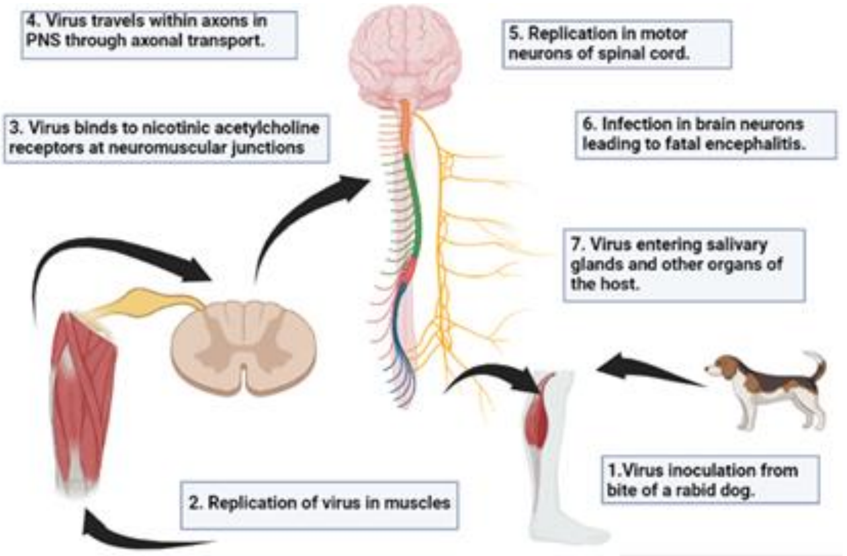
4. Virus travels within axons in PNS through axonal transport.
5. Replication in motor neurons of spinal cord.
3. Virus binds to nicotinic acetylcholine receptors at neuromuscular junctions
6. Infection in brain neurons leading to fatal encephalitis.
7. Virus entering salivary glands and other organs of the host.
1.Virus inoculation from bite of a rabid dog.
2. Replication of virus in muscles

Fig. 2: The complete pathogenesis of the RABV.

Vaccination

Rabies has no medicinal cure, except supportive therapy. Rabies is always fatal if it goes untreated or is treated incorrectly because the purpose of supportive care is to lessen the patient's pain. These days, rabies can only be controlled by the management of stray animals, mostly by the management of stray dogs (Wilkins and Piero 2007; Blancou 2008; Rupprecht et al. 2008;). After management proper vaccination is the key to controlling the outbreak of rabies. Due to the lack of proper vaccination and no check and balance on stray dog’s vaccination, rabies is a burning issue (Singh et al. 2017). Giving a person an injection of rabies immune globulin and another injection of the rabies vaccine as soon as possible after being bitten by an infected animal or coming into contact with its saliva can stop rabies before the latent symptoms develop. The right timing and the patient's ability for a significant immune response are crucial to patient survival. The vaccination schedule is different for pre-exposure and pot-exposure cases (Soentjens et al. 2019). For those at risk of exposure to rabid animals, pre-exposure prophylactic immunization is advised. Pre-exposure immunization is necessary for your lovely pets, and stray animals and for the persons coming in contact with this deadly virus in any way (Rupprecht et al. 2006).

The WHO advises all staff members who handle suspected or known contaminated materials to get preventive immunizations. A routine immunization program should be considered by veterinarians, animal handlers, and laboratory staff (Monaco et al. 2006). People going to places where dog rabies is endemic and who won't have easy access to medical treatment should consider getting immunized before traveling. Pre-exposure immunization helps in the development of immunity by the host immune system. But if you or your animal gets a bite by a rabid animal, then post-exposure vaccination is necessary to save lives. After thorough washing of the wound or scratches with soap, a total of 6 doses of rabies immunoglobulins are given within 28 days. Because it prevents the virus and slows or stops viral propagation through the nerves. Human rabies immune globulin is applied to or administered intravenously at the site of the bite as soon as possible. By inducing the immune

Table 4: The pre- and post-exposure vaccination schedule (Fogelman et al. 1993).

No.	Pre-exposure vaccination	Post-exposure vaccination
1	Dose 1: 1 ml (IM), at 0 days.	No previous vaccine history then 1ml (IM) vaccine at 0, 3, 7, 14, 30, and 90th days after the bite.
2	Dose 2: 1ml (IM), 7 days after dose 1	Vaccine history within one year then 1ml (IM) vaccine at 0 and 3rd day after the bite.
3	Dose 3: 1ml (IM) between 21 or 28 days after dose 1.	Vaccine history between 1-5 years then 1ml (IM) vaccine at 0, 3, and 7th days after the bite.

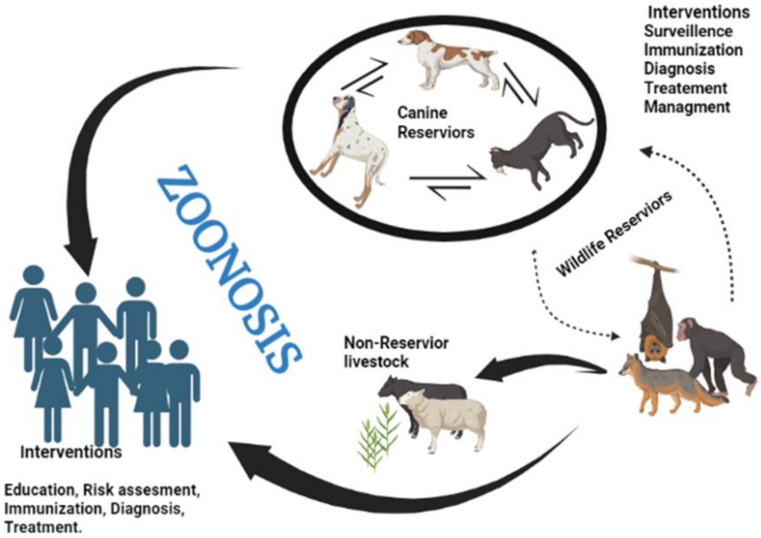

Fig. 3: The zoonotic transmission chain of Rabies.

system of the body to develop antibodies to fight the rabies virus, the vaccine protects against rabies. The pre-and post-exposure vaccination schedule for rabies prevention is described in the veterinary Merck manual as shown in Table 4 (Fogelman et al. 1993).

The three types of rabies vaccines available for use on animals are recombinant vaccines, chemically or physically inactivated vaccines, and live attenuated vaccines. Inactivated virus vaccines are also used on the human side (Lau and Hohl 2013).

Zoonotic Impact and One Health

Rabies is a fatal zoonotic disease, so the only way to control this deadly disease is the one health approach (Fig. 3). We must connect and manage the animals, humans, and the environment surrounding them to control this virus and break the transmission chain of this ancient disease. Roughly fifty-nine thousand human beings die of this disease annually throughout the globe. Rabies is not only transferred by canines, but bats and other feral animals are also a potent source of this disease transfer, as they are all the reservoir hosts for this virus. Rabies can transmit in humans either by the bite of a rabid dog, cat, or any feral mammal, and it is 100% fatal once clinical signs appear (Pieracci et al. 2019).

Under the flag of one health, "Zero by 2030" is an international slogan followed by all countries, which is proposed by the World health organization. This slogan means that zero cases of rabies will be reported by the year 2030 (Bonilla-Aldana et al. 2023). For successful results of this slogan, they are maintaining the environment, making it free from any kind of rabies virus aerosols, vaccinating the animals and humans, and keeping a check on the population of stray canines. 99% of human rabies cases are reported due to the bite of the canines (Agarwal and Reddajah 2004). By following this approach Bangladesh reduces the number of deaths due to rabies from 1500 to only 200 in just three years, from 2012-2015 (Gongal and Wright 2011).

To control this zoonotic impact of rabies, the control of animals, mostly stray dogs, is very important. One Health strategy has been effective in several other countries, including Bhutan, Sri Lanka, and Bangladesh. Between 2006 and 2016, just seventeen cases of rabies were reported in Bhutan (Tenzin et al. 2017). By proper vaccination of stray animals, this disease is under control in developed countries. But in under-developed countries like Nepal, India, and Pakistan, this disease is still prevalent due to a lack of proper vaccination, a high population of stray dogs roaming on the streets, and a lack of awareness. Applying one health rule for rabies eradication is the ultimate solution to control rabies (Leung and Davis 2017).

Rabies in other Species

The structure of the rabies virus is unique which enables it to infect almost all mammals. But the change in habitats, different life cycles, and change in their method to interact with other species along with their likelihood to bite make some mammals' reservoir hosts the dead-end host. The bovines, equines, and other domesticated animals act as dead-end hosts because of a lack of biting habits. Whereas biting and aggressive animals like canines, felines, foxes, and raccoons act as reservoir hosts. They can reserve viruses in their populations and sporadically transfer to other animals simply by biting and rarely by scratching. Rabies causes acute encephalitis and is a deadly disease. It is confirmed by many theories that the Lyssavirus mainly originates from the population of old-world bats, which act as a reservoir host for about 14-16 known viruses (Rupprecht et al. 2011). All reservoir hosts develop their virus variant which circulates within that species but is also capable of spreading disease to other species. Rabies lyssavirus or RABV is considered the main species responsible for the disease transmission in different species among the 16 recognized species of the genus lyssavirus (Marston et al. 2018). Globally rabies is maintained in the ecosystem by both sylvatic and urban cycles. In the urban cycle, domestic dogs play the major role of reservoir host. While in a sylvatic cycle which is most important in new world rabies transmission, bats and wild canines like a fox, raccoons, mongooses, and coyotes serve as reservoir hosts (Devleesschauwer et al. 2016).

Other warm-blooded animals like birds can be infected experimentally, and one case study from India shows the evidence of natural acquisition of rabies by domestic fowl following a dog bite (Julie et al. 2015). Although the major signs and symptoms of rabies are similar among all animals such as nervous manifestation and associated behavioral changes, some species variations also occur, as described in the Veterinary Merck Manual (Table 5).

Global Epidemiology of RABV

Rabies is caused by a deadly virus (Balcha and Abdela 2017). It is of more importance because it can cause a mass number of deaths annually. Developed countries have effectively controlled rabies by minimizing the chances of dog-related rabies (Wunner and Briggs 2010). In the US annual human deaths due to rabies have decreased by 99% as compared to the 1900s and more than 90% of rabies cases occur in wildlife (Yousaf et al. 2012). Although sylvatic rabies is still found in developed countries some countries (mostly isolated islands) have successfully eradicated rabies. These rabies-free countries are the United Kingdom, Japan, Ireland, Australia, and New Zealand (Kwan et al. 2017). The urban cycle of rabies involving domestic dogs as the reservoir host is the main cause of rabies in underdeveloped nations. Unfortunately, each year 59000 people die due to rabies across the world mostly due to dog bites, and South Asian Association for Regional Cooperation (SAARC) countries comprises about 45% part of this number and the remaining occurs in central Asia, Africa, and the middle east (Hampson et al. 2015). This is due to poor policy making, lack of awareness, and vaccination facilities. Another dark side of human rabies is that almost half of the deaths occur in children below the age of 15 years (World Health Organization 2010).

35000 deaths are reported in Asia's Urban areas per year, while Alone India stands for about 60% of deaths in Asia (Pantha et al. 2020). Central Asia reported hundreds of deaths. Rabies prevalence among countries is given in Table 6 (Gongal and Wright 2011).

Besides human rabies, developing countries also face huge economic losses due to the death of domestic animals by rabies (Regea 2017). From an epidemiological point of view in Asian and African regions after dogs, cattle, and sheep, goats are the most affected domestic species followed by equines (Hikufe et al. 2019). In Arab countries, camelids are most affected. In Nepal, bovines are even more affected than dogs. While in developed countries bats are the leading host of rabies and then come to the wild canines (Kuzmin et al. 2011). Cats are more likely to be affected by rabies in these countries because they are less considered to be vaccinated against the disease (Wang et al. 2009).

Yet, there are a few countries that are free from rabies. Either they are the islands, as viruses can’t transfer through oceans that’s why they are free from it (Dietzschold et al. 2003). While other developed countries eradicate rabies by mass immunization of humans and animals, surveillance of the population of dogs, and by making good pre-and post-exposure prophylaxis strategies. Rabies-free zones are listed in Table 7.

Research Studies and Innovations in Rabies

Till today there are no effective treatments for rabies, rather preventive measures, and post-exposure prophylaxis (PEP) are the only ways to handle it. Future research aims at the goal of discovering an effective drug for the treatment of rabies (Madhusudana et al. 2013). Efforts are being made to develop a combination treatment protocol for rabid dogs. By using advanced molecular techniques and understanding the host-virus interaction, one medicine treatment protocol can be developed for both animals and humans. Studies are being made to understand the virus structure, discover better adjuvants, and genetically modify the virus to make more advancements in vaccine preparation (Anthony et al. 2019).

Once the symptoms of rabies appear in an individual the approximate chance of its survival is zero to none (Nigg and Walker 2009). Despite the existence of effective vaccines thousands of people annually die due to rabies. Costly vaccines, their unavailability, and lack of awareness are the major limiting factors in the way of global eradication of rabies. Therefore, scientists are in a continuous search for a better solution. Recently IZSVe (institu zooprofilattico sperimentale delle Venezie) with the collaboration of other international research institutes has identified and characterized two broad-spectrum monoclonal antibodies. It has shown great efficacy for longer durations against rabies

Table 5: Different signs and symptoms of Rabies in different species.

No.	Species	Signs of Rabies
1	Cattle	Milk production abruptly drops, abnormally alert cows, increased eye and ear responses, abnormal bellowing.
2	Equines	Colic-like signs like rolling, distress, and agitation, highly responsive, alert.
3	Sheep and goat	Ptyalism, restlessness, aggression.
4	Camelids	The dumb form is more common, recumbency, ptyalism, hypersexuality, and biting behavior.
5	Bats	Nocturnal behavior diminishes, lying motionless, unable to fly.
6	Raccoons, foxes and coyotes	Act like diurnal animals, have ataxia and aggression, don't fear humans, and attack animals
7	Rodents	Rarely infected, common in lab-reared.

Table 6: The Global status of RABV.

No.	Name of country	Status of Rabies	References
1	Africa	2011, 20,000 deaths annually.	(Ahmad et al. 2018).
2	European Union	2011 (9 cases of Rabies), 2014 (3 cases of human rabies).	(Gongal and Wright 2011).
3	Thailand	2011- less than 25 human deaths by rabies. 2018 only 17 human deaths by rabies, and 40,000 dog bite cases.	(Gongal and Wright 2011)
4	Vietnam	2011- 350,000 dog bite cases, 80 human deaths.	(Lee et al. 2018).
5	Chongqing	2007-2016, 809 fatal human deaths by rabies.	(Davlin and VonVille 2012).
6	Bhutan	1996-2009, 814 human deaths by rabies. 2011- less than 10% of human deaths cases by rabies	(Gongal and Wright 2011).
7	Bangladesh	2011- 300,000 dog bite cases, 2000-2500 human deaths by rabies.	(Gongal and Wright 2011).
8	Pakistan	2011- Human rabies cases range between 2000-5000.	(Gongal and Wright 2011).
9	India	2011- human rabies cases range from 18,000-20,000.	(Acharya et al. 2020)

Table 7: The Rabies-free areas of the world.

No.	Rabies-free zones	References
1	Maldives (island, no transmission of virus through oceans)	(Gongal and Wright 2011).
2	Australia and pacific islands (island, no transmission of virus through oceans along with proper immunization of dogs)	(Gongal and Wright 2011).
3	Canada, USA, Japan (no dog-mediated rabies)	(Ruiz et al. 2010).
4	Countries in South and North America like Columbia, Panama, Uruguay, Costa Rica, Belize, and Chile (good post-exposure prophylaxis along with vaccination of stray dogs)	(Vigilato et al. 2013)

and related Lyssa viruses. This antibody cocktail has more potency to fight the rabies virus and is also in an affordable range (Benedictis et al. 2016).

Dumb and paralytic forms and species variations make it difficult to diagnose rabies in animals. Many tests have been developed to diagnose rabies but there is a question mark on their accuracy. Recently the PCR test has been developed and is considered more efficient. But still, these tests are very time-consuming and need advanced expertise and requirements. That's why NCEZID (National center for emerging and zoonotic infectious Diseases) has developed a new PCR-based test. This test is quicker and more accurate and requires fewer requirements and expertise than the previous ones (Artika et al. 2020).

Research and development of certain therapeutic components, particularly viral inhibitors, and neuroprotectant medicines, benefit greatly from preclinical studies of RABV infection. One medical approach is proven beneficial. One therapeutic agent development for both canines and human rabies as the pathogenic cycle of rabies is the same in both (Davlin and VonVille 2012). There are many ways that the care given to canine patients by veterinarians can be paralleled to critical care and supportive therapy given to patients in clinical settings.

In areas where rabies is in endemic form, dogs were caught and killed just for the safety of humans (Srinivasan et al. 2019). These dogs can be used for the preclinical and clinical studies of RABV infections and proved helpful in the development of one medicine. Even if the therapeutic event fails, these dogs will be euthanized after appropriate palliative medication and care (Mani et al. 2019).

Control Policies Worldwide

Global organizations like the Food and Agriculture Organization (FAO), the World organization for animal health (WOAH), Global Alliance for Rabies Control (GARC), and the World health organization (WHO) are aimed to end human rabies associated with dogs in 2030. For this "Zero by thirty" goal achievement investments are being raised and applied to control rabies in developed as well as developing countries (WHO Rabies Modelling Consortium 2020). The control strategies involve mass vaccination of dogs, active disease reporting and surveillance, canine population control, and awareness about disease transmission and control (Pantha et al. 2020). The Control strategies are shown in Fig. 4.

Developed countries had already controlled rabies through mass vaccination of dogs, traveling restrictions of animals, and total check of vaccination records. For wild reservoirs of rabies mass, oral vaccinations are currently deployed.

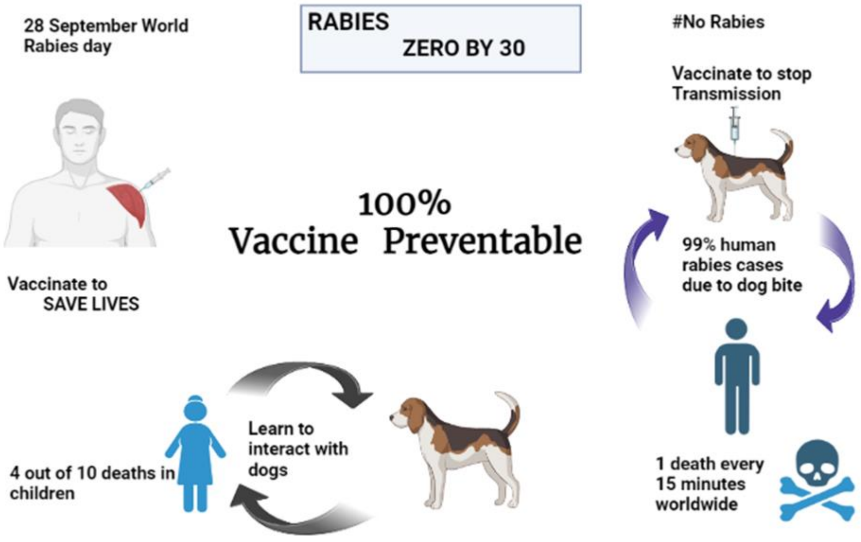
28 September World Rabies day
RABIES ZERO BY 30
#No Rabies
Vaccinate to stop Transmission
100% Vaccine Preventable
Vaccinate to SAVE LIVES
99% human rabies cases due to dog bite
Learn to interact with dogs
4 out of 10 deaths in children
1 death every 15 minutes worldwide

Fig. 4: Control strategies under the WHO slogan "ZERO-BY-30"

Effective management of the stray dog population by NGOs and shelter homes has also played a major role in the elimination of rabies in these countries (Andres et al. 2017). These countries further aim to maintain the status and put a check on wildlife reservoirs of rabies to avoid any outbreak in the future.

In Asia, India is the most affected country with rabies contributing to 60% of the total dog-mediated deaths of humans in Asia (Ward 2012). It has applied control strategies like CVD (capture-vaccinate-release) and DD (door-to-door vaccination) to control canine rabies (Acharya et al. 2021). According to GARC, Pakistan scores 1.5 out of 5 on the Stepwise approach toward Rabies Elimination (SARE) scale. In Pakistan, approximately 450 human deaths per year occur due to rabies and there is no national policy or one health working force for rabies. Nevertheless, a system of online reporting for dog bites, dog registration, and control has been launched in the country's capital city. Thailand has also controlled its stray dog rabies population by using oral rabies vaccines and effectively avoided any new outbreak of rabies by achieving 65% coverage (Chanachai et al. 2021). From 2006-2016, Bhutan reported only 17 cases of rabies by applying the One health approach. Bangladesh reduces its rabies death number from 1500 to 200 in just three years (Acharya et al. 2020).

The world has now understood the importance of the concept of One Health in the control and eradication of zoonotic diseases (Cleaveland et al. 2014). With proper strategy and resources, a lethal disease like rabies can be eradicated from the World.

Conclusion

Rabies is a zoonotic and deadly disease but it is preventable. It is mainly transmitted by the bite of a rabid dog. After a bite, the virus travels toward the central nervous system causing fatal encephalitis. Once the clinical signs appear, there is no treatment. Utilizing proper vaccination, its incidence in humans and animals decreases. Rabies has a great zoonotic impact, as it affects both humans and animals, leading to economic as well as social losses. Rabies is not only a canine disease but different species like cattle, sheep, goats, and felines are equally susceptible. The developed countries developed the control strategies and now they have minimum cases of rabies reported. While under-developed countries are still struggling to get rid of this disease. The world under the guidance of the World health organization is working to eradicate this ancient disease under the slogan "Zero by 30". One health approach is used to eliminate rabies by connecting and managing humans, animals, and their environment. By applying the strategies designed by the World Health Organization under the flag of one health, countries like the US, Thailand, and Australia are considered Rabies free zones. The world has now understood the importance of the concept of One Health in the control and eradication of zoonotic diseases. With proper strategy and resources, a lethal disease like rabies can be eradicated from the World. But due to a lack of proper awareness and resources, under-developed countries like Asia and Africa are still in the vortex of fear of this deadly disease.

REFERENCES

Acharya KP et al., 2020. One-health approach: A best possible way to control rabies. One Health 10: 100161.

Acharya KP et al., 2021. Rabies control in South Asia requires a One Health approach. One health (Amsterdam, Netherlands) 12: 100215.

Afonso CL et al., 2016. Taxonomy of the order Mononegavirales: update 2016. Archives of Virology 161(8): 2351–2360.

Agarwal N and Reddajah VP, 2004. Epidemiology of dog bites is a community-based study in India. Tropical doctor 34(2): 76-78.

Ahmad T et al., 2018. Rabies in Asian countries: where do we stand? Biomedical Research and Therapy 5(10): 2719–2720.

Artika IM et al., 2020. Pathogenic viruses: Molecular detection and characterization. Infection, Genetics, and Evolution 81: 104215.

Albertini AA et al., 2011. Rabies virus transcription and replication. Advances in Virus Researches 79: 1–22.

Andres VV et al., 2017. Successful strategies implemented toward the elimination of canine rabies in the Western Hemisphere. Antiviral Research 143: 1-12.

Anthony R et al., 2019. Animal and Plant Health Agency, Weybridge, Surrey, UK. Vaccine 37 (1): 140–145.

Leung T and Davis SA, 2017. Rabies vaccination targets stray dog populations. Frontiers in Veterinary Science 4: 52.

Baer GM, 2012. Pathogenesis to the central nervous system. The Natural History of Rabies 1: 181-198.

Badrane H and Tordo N, 2001. Host switching in Lyssavirus history from the Chiroptera to the Carnivora orders. Journal of Virology 2001: 8096–8104.

Balakrishnan S, 2018. Knowledge level and attitude on rabies and dog bite management among rural people. Journal of Entomology and Zoology Studies 6: 1963-1967.

Balcha C and Abdela N, 2017. Review of rabies prevention and control. International Journal of Public Health Science 6(4): 343-350.

Blancou J, 2008. The control of rabies in Eurasia: overview, history, and background. Developmental Biology (Basel) 131: 3–15.

Blanton JD et al., 2009. Rabies surveillance in the United States during 2008. Journal of the American Veterinary Medical Association 2009: 676-689.

Bonilla-Aldana DK et al., 2023. Zero by 2030 and OneHealth: The multidisciplinary challenges of rabies control and elimination. Travel medicine and infectious disease 51.

Both L et al., 2012. Passive immunity in the prevention of rabies. Lancet Infectious Diseases 12(5): 397–407.

Boulger LR and Porterfield JS, 1958. Isolation of a virus from Nigerian fruit bats. Transactions of The Royal Society of Tropical Medicine and Hygiene 1958: 421–424.

Campos AAS et al., 2002. Franco.Rabies surveillance in wild mammals in the south of Brazil. Transboundary Emergency Diseases 2002: 906-913.

Cleaveland S et al., 2014. Rabies control and elimination: a test case for One Health. Veterinary Record 175(8): 188-193.

Chanachai K et al., 2021. Feasibility and effectiveness studies with oral vaccination of free-roaming dogs against rabies in Thailand. Viruses 13(4): 571.

Daniel G et al., 2004. Overview, Prevention, and Treatment of Rabies. Mayo Clinic Proceedings 79(5): 671-676.

Dietzschold B et al., 2003. New approaches to the prevention and eradication of rabies. Expert Review of Vaccines 2(3): 399-406.

Benedictis D et al., 2016. Development of broad-spectrum human monoclonal antibodies for rabies post-exposure prophylaxis. European Molecular Biology Organization, Molecular Medicine 8(4): 407-421.

Devleesschauwer B et al., 2016. Epidemiology, impact and control of rabies in Nepal: a systematic review. The Public Library of Science Neglected Tropical Diseases 10(2): e0004461.

Davlin SL and VonVille HM, 2012. Canine rabies vaccination and domestic dog population characteristics in the developing world: a systematic review. Vaccine 30(24): 3492-3502.

Briggs DJ, 2012. The role of vaccination in rabies prevention. Current Opinion in Virology 2(3): 309–314.

Pantha S et al., 2020. Review of rabies in Nepal. One Health 10: 100155.

Pieracci EG et al., 2019. Vital signs: Trends in human rabies deaths and exposures — United States, 1938–2018. Morbidity and Mortality Weekly Report 68: 524-528.

Feder HM et al., 2012. Rabies: still a uniformly fatal disease? Historical occurrence, epidemiological trends, and paradigm shifts. Current Infectious Disease Report 14(4): 408–422.

Fekadu M et al., 1988. Pathogenesis of rabies virus from a Danish bat (Eptesicus serotinus): neuronal changes suggestive of spongiosis. Archives of Virology 99(3): 187-203.

Fogelman V et al., 1993. Epidemiologic and clinical characteristics of rabies in cats. Journal of the American Veterinary Medical Association 202: 1829-1838.

Fooks AR et al., 2014. Current status of rabies and prospects for elimination. Lancet 384: 1389–1399.

Gongal G and Wright AE, 2011. Human rabies in the WHO Southeast Asia region: forward steps for elimination, Advances in Preventive Medicine 2011: 1–5.

Lee HS et al., 2018. Geographical and temporal patterns of rabies post-exposure prophylaxis (PEP) incidence in humans in the Mekong River Delta and southeast central coast regions in Vietnam from 2005 to 2015. Public Library of Science One 13(4): e0194943

Hankins DG and Rosekrans JA, 2004. Overview, prevention, and treatment of rabies. Mayo Clinical Proceedings 2004: 671–676.

Hemachudha T et al., 2002. Human rabies: a disease of complex neuropathogenic mechanisms and diagnostic challenges. Lancet Neurology 1: 101–109.

Hemachudha T et al., 2013. Human rabies: neuropathogenesis, diagnosis, and management. Lancet Neurology 12(5): 498–513.

Hampson K et al., 2015. Estimating the global burden of endemic canine rabies. The Public Library of Science Neglected Tropical Diseases 9(4): e0003709.

Hikufe EH et al., 2019. Ecology and epidemiology of rabies in humans, domestic animals and wildlife in Namibia, 2011-2017. PLoS Neglected Tropical Diseases 13(4): e0007355.

Jackson AC et al., 2013. Pathogenesis. In: Jackson AC, editor. Rabies (3rd Edition): Academic Press; pp: 299-349.

Jackson AC, 2010. Rabies pathogenesis update. Revista Pan-Amazônica de Saúde 1(1): 167–172.

Jackson, 2016. Human Rabies, a 2016 Update. Current Infectious Diseases Reports 2016: 18–38.

Jackson AC, 2003. Rabies virus infection: an update. Journal of Neurovirology 9(2): 253-258.

Julie et al., 2015. Natural Rabies Infection in a Domestic Fowl (Gallus domesticus): A Report from India. Public Library of Science Neglected Tropical Diseases 9(7): e0003942.

Kwan NCL et al., 2017. Quantitative risk assessment of the introduction of rabies into Japan through the importation of dogs and cats worldwide. Epidemiology and Infection 145(6): 1168-1182.

Kelly RM and Strick PL. 2000. Rabies as a transneuronal tracer of circuits in the central nervous system. Journal of Neuroscience Methods 103(1): 63–71.

Koyuncu O er al., 2013. Virus infections in the nervous system. Cell Host and Microbe 13(4): 379-393.

Kuzmin IV et al., 2011. Bats, emerging infectious diseases, and the rabies paradigm revisited. Emerging Health Threats Journal 4(1): 7159.

Lafon M, 2011. Evasive strategies in rabies virus infection. Advances in Virus Research 79: 33-53.

Lau CL and Hohl N, 2013. Immunogenicity of a modified intradermal pre-exposure rabies vaccination schedule using a purified chick embryo cell vaccine: an observational study. Travel Medicine and Infectious Disease 11(6): 427–430.

Lewis P et al., 2000. Rabies virus entry at the neuromuscular junction in nerve–muscle cocultures. Muscle and Nerve: Official Journal of the American Association of Electrodiagnostic Medicine 23(5): 720-730.

Lumio J et al., 1986. Human rabies of bat origin in Europe. Lancet 1986: 378.

Ruiz M and Chávez CB, 2010. Rabies in Latin America. Neurology Residency 32(3): 272–277.

Madhusudana SN et al., 2013. Feasibility of reducing rabies immunoglobulin dosage for passive immunization against rabies: results of In vitro and In vivo studies. Human Vaccine and Immunotherapeutics 9(9): 1914–1917.

Marston DA et al., 2018. The lyssavirus host-specificity conundrum—rabies virus—the exception not the rule. Current Opinion in Virology 28: 68-73.

Mani RS et al., 2019. Case reports survival from rabies: case series from India. American Journal of Tropical Medicine and Hygiene 100: 165–169.

Mazarakis ND et al., 2001. Rabies virus glycoprotein pseudotyping of lentiviral vectors enables retrograde axonal transport and access to the nervous system after peripheral delivery. Human Molecular Genetics 10(19): 2109-2121.

McCall BJ et al., 2000. Potential exposure to Australian bat lyssavirus, Queensland, 1996-1999. Emerging Infectious Diseases 2000: 259–264.

Mebatsion T et al., 1999. The matrix protein of the rabies virus is responsible for the assembly and budding of bullet-shaped particles and interacts with the transmembrane spike glycoprotein G. Journal of Virology 73(1): 242–250.

Meredith CD et al., 1971. An unusual case of human rabies thought to be of chiropteran origin. South African Medical Journal 45(28): 767–769.

Monaco F et al., 2006. Studies on an inactivated vaccine against rabies virus in domestic animals. Developmental Biology (Basel) 125: 233–239.

Moore SM and McVey DS, 2022. Rhabdoviridae. Veterinary Microbiology 2022: 609-621.

Nigg AJ and Walker PL, 2009. Overview, prevention, and treatment of rabies. Pharmacotherapy 29: 1182–1195.

Pantha S et al., 2020. Review of rabies in Nepal. One Health 10: 100155.

Ridder A et al., 2016. 2016: the beginning of the end of rabies? The Lancet Global Health 4(11): 780-781.

Regea G, 2017. Review on the economic importance of rabies in developing countries and its controls. Archives of Preventive Medicine 2(1): 15-21.

Rupprecht CE et al., 2002. Rabies re-examined. Lancet Infectious Diseases 2: 327-343.

Rupprecht CE et al., 2006. Current and future trends in the prevention, treatment, and control of rabies. Expert review of Anti-infective Therapy 4(6): 1021-1038.

Rupprecht CE et al., 2008. Can rabies be eradicated? Developmental Biology (Basel). 131: 95–121.

Rupprecht CE et al., 2011. A perspective on lyssavirus emergence and perpetuation. Current Opinion in Virology 1: 662–670.

Singh R et al., 2017. Rabies–epidemiology, pathogenesis, public health concerns and advances in diagnosis and control: a comprehensive review. Veterinary Quarterly 37(1): 212-251.

Schneider LG and Cox JH, 1994. Bat lyssaviruses in Europe. Lyssaviruses: Springer-Verlag, Berlin; pp: 207–218.

Srinivasan K et al., 2019. Reorienting rabies research and practice: Lessons from India. Palgrave Communications *5*(1): 1-11.

Shope RE et al., 1970. Two African viruses are serologically and morphologically related to the rabies virus. Journal of Virology 6(5): 690–692.

Susilawathi NM et al.,2012. Epidemiological and clinical features of human rabies cases in Bali 2008-2010. BMC Infectious Diseases 12(1): 1-8.

Soentjens P et al., 2019. Preexposure intradermal rabies vaccination: a noninferiority trial in healthy adults on shortening the vaccination schedule from 28 to 7 days. Clinical Infectious Diseases 68(4): 607-614.

Tenzin T et al., 2017.Community-based survey during rabies outbreaks in Rangjung town, Trashigang, eastern Bhutan, 2016. BMC Infectious Diseases 17(1): 281.

Vigilato MAN et al., 2013. Espinal, Progress towards eliminating canine rabies: policies and perspectives from Latin America and the Caribbean. Philosophical Transactions of the Royal Society B. Biological Sciences 368 (1623): 20120143.

Ward MP, 2012. Review of rabies epidemiology and control in South, South East, and East Asia: past, present and prospects for elimination. Zoonoses and Public Health 59(7): 451-467.

Wang X et al., 2009. Animal rabies in Massachusetts, 1985–2006. Journal of Wildlife Diseases 45(2): 375-387.

Wilde H et al., 2013. Rabies in Asia: the classical zoonosis. One health: the human-animal-environment interfaces in emerging Infectious Diseases: Springer-Verlag, Berlin; pp: 185–203.

Wilkins PA and Piero FD, 2007. Rabies. Equine Infectious Diseases 2(19): 185–191.

World Health Organization, 2010. Rabies vaccines: WHO position paper. Weekly Epidemiological Record 85(32): 309-320.

WHO Rabies Modelling Consortium, 2020. Zero human deaths from dog-mediated rabies by 2030: perspectives from quantitative and mathematical modeling. Gates Open Research 3: 1564.

Wunner WH and Briggs DJ, 2010. Rabies in the 21st Century. PLOS neglected tropical diseases 4(3): 591.

Xianfu Wu et al., 2002. Both viral transcription and replication are reduced when the rabies virus nucleoprotein is not phosphorylated. Journal of Virology 4153-4161.

Yousaf MZ et al., 2012. Rabies molecular virology, diagnosis, prevention, and treatment. Virology Journal 9: 1–5.

Zhu S and Guo C, 2016. Rabies control and treatment: From prophylaxis to strategies with curative potential. Viruses 8(11): 279.

18

Public Health Risks Associated with Norovirus Gastroentritis

AUTHORS DETAIL

Sara Ijaz[1*], Shama Jamel[2], Ammar Faiz[3], Abdullah Alsayeqh[4], Aiman Mushtaq[5], M. Faizan Elahi Bhatti[1], Khushbakht Asad[5]

[1]Department of Epidemiology and Public health, University of Veterinary and Animal Sciences, Lahore, Pakistan
[2]Department of Pathology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[3]Department of Meat science and technology, University of Veterinary and Animal Sciences, Lahore, Pakistan
[4]Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, Qassim University, Buraidah 51452, Qassim, Saudi Arabia
[5]University of Veterinary and Animal Sciences, Lahore, Pakistan
*Corresponding author: saraijaz0306@gmail.com

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INTRODUCTION

Globally, gastroenteritis is a serious public health concern. Norovirus is currently identified as the primary reason for nonbacterial, acute gastroenteritis in individuals and is categorized as an emerging disease.

Four genera are included in the family Calciviridae, which were given names based on disease characteristics. The two genera were named after vesicular lesions (Vesivirus and Lagovirus), while the other two genera were named after the infected hosts and the location of the first isolation of these species (Sapporo, Japan—Sapovirus; Norwalk, USA—Norovirus), (Cheetham et al. 2006).

The viruses of this family are microscopic and non-enveloped, with an approximate diameter ranging from 27-35 nm. Norovirus is a single-stranded positive-sense RNA virus. They infect a wide range of hosts, including humans, pigs, cattle, dogs, and mink. They can cause a wide range of diseases and lesions in humans, such as digestive tract infections in human beings and animals like pigs, cattle, dogs, and mink etc. Pigs, sea lions, and other marine mammal species could be infected with vesicular lesions, while reproductive failure, stomatitis, upper respiratory tract infection, and hemorrhagic and systemic diseases occur in cats. The original strain of Nov, known as Norwalk virus (NV), was first identified in 1968 and linked to a human gastroenteritis outbreak in Norwalk, Ohio, which was named Norwalk virus (Nov prototype strain) in 1968 (Caul 1996).

Numerous studies show that BoNoVs are frequently found in cattle and occasionally at high frequency in cases of diarrhea in various countries, despite the fact that they have been studied much less than other viruses that are known to be the cause of NCD (neonatal calf diarrhea), such as rotavirus and coronavirus (Castells et al. 2020).

Acute norovirus infection is characterized by nausea, vomiting, diarrhea, stomach cramps, headache, myalgia, and high temperature. Vomiting is frequently projectile and intense (Caul 1996). Norovirus can develop chronic dehydrating diarrhea in immunocompromised patients, which can cause significant consequences and occasional fatality of up to 25% (Frange et al. 2012).

Epidemiology and Prevalence

Both sporadic infections and outbreak cases of acute gastroenteritis are frequently caused by noroviruses. Large epidemics frequently happen in public places like hospitals, nursing homes for the elderly and daycare centers (Matthews et al. 2012).

Noroviruses can be divided into five genogroups based on their considerable genomic diversity. There are at least 30 distinct genotypes that are further divided into three pathogenic genogroups (GI, GII, and GIV) of humans. Drift variations of genotype II have been responsible for many global epidemics (Siebenga et al. 2009).

National surveillance data of norovirus gastroenteritis in Germany are accessible in an electronic database at the Robert Koch Institute, which is the country's public health institute (Jor et al. 2010; Otto et al. 2011). Many epidemiological studies have shown that NoVs are commonly found in humans in addition to those of the bovine, pig and murine species (mice and rats). Few investigations on animal NoV infections have been conducted, and the epidemiology is poorly characterized (Cheetham et al. 2006).

Norovirus is responsible for 60% of cases of acute gastroenteritis in the country, or around 21 million episodes, across the year, as it is stated, by The United States' Centers for Disease Control and Prevention (CDC). Norovirus has also been involved in sporadic disease as an outcome of the inclusion of molecular techniques. Norovirus detection by Reverse transcriptase PCR (RT-PCR) conferred 5 to 31% of reports of gastroenteritis in hospitalized patients and an additional 5 to 36% of reports in patients seeking outpatient assessment (Patel et al. 2008).

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Pathogenesis

The mechanism of disease spread in man and animals is not fully understood. This disease persists for 1-2 days. Acute enteritis with non-hemorrhagic diarrhea, vomiting, lack of appetite, gut ache, and slightly high body temperature are symptoms of infection. The ailment is self-limiting and lasts only 12-60 hours; however, immune-compromised animals may have chronic diarrhea and shed the virus for months or years (Karst et al. 2015).

The primary target cells for virus duplication are mainly intestinal cells of the anterior part of the intestinal tract, causing malabsorption and diarrhea. The intestinal epithelium seems to be unaffected, but the jejunum has developed specific histo-pathological lesions caused by human Nov infection, such as intestinal villi atrophy, intestinal epithelial cell breakdown, hyperplasia of crypt cells, and vacuolated and mononuclear inflammatory infiltrate in the lamina propria of villi. The shortened microvilli and reduced brush border enzyme activity that happen in acute infection related to the mal-absorption (Karst et al. 2015).

Both diarrheal and non-diarrheic cattle fecal samples contain bovine NoV. Newborn Infected calves exhibit diarrhea after 3-4 days of infection, which lasts for only one day. Diseased calves display a lack of appetite on the fourth and fifth day of infection, non-hemorrhagic inflamed intestine, mal-absorption, and discrete diarrhea at the age of 1-8 years in calves. Heartbeats and rate of breathing were maintained within normal ranges, and the temperature of rectum ranges between 37 and 40°C (Jor et al. 2010; Otto et al. 2011). Degeneration of villous and elongation of crypts in the anterior part of small intestine result from infections with bovine NoV genotypes (Hall et al. 1984; Otto et al. 2011).

Bovine NoV GIII.1 infects all entero-absorptive cells, in contrast to other intestinal viruses like bovine rotavirus and norovirus, which mainly infect the tips and bases of villi. It has been hypothesized that the severe villus degeneration and loss of mature intestinal cells caused by the bovine NoVGIII.1 may shorten the duration of infection because fewer cells are available to become infected. However, experimental studies using the bovine GIII.2 strain demonstrated that calves shed the virus in feces for at least 30 days after giving challenge, irrespective of the fecal condition (diarrheic or not) and the length of clinical manifestations (Jor et al. 2010). Bovine NoV GIII 2 was seen in the calves without showing significant histological changes such as villous atrophy, mortification of intestinal cells, and diarrhea. (Jung et al. 2014).

The importance of porcine NoV is still unclear as a cause of diarrhea in pigs. The porcine NoV incubation period in an experimental challenge of piglets was only a day post-inoculation, and diarrhea lasted for 2-6 days. Piglets' small intestines displayed mild to moderate villous atrophy as well as mild to moderate and multifocal villous fusion (Shen et al. 2012).

Piglets were injected with the human NoV strain GII as part of the experiment. The diarrhea was less severe and self-inductance, lasting for one to three days, and the incubation period ranged from 24 to 48 hours. Additionally, it was found that the virus shed lasted for only 1-4 days. The cytoplasm of the small intestine cells contained the virus antigen. There was multifocal degeneration of the intestinal villi, which affected the morphology of intestinal cells and low-intensity histo-pathological lesions. An additional finding of this research was the rise in enterocytes that had undergone apoptosis (Cheetham et al. 2006).

NoV reduplication might not be limited to intestinal cells. The only norovirus that replicates in vitro among all the latent experimental studies investigated to better understand the mechanism of disease proliferation of noroviruses is the murine NoV. This agent reproduces in bone marrow cell cultures, mouse macrophage cell lines and dendritic cells derived from cultures of macrophages and bone marrow. Recombination-activating gene 2 (RAG2) and signal transducer and activator of transcription 1 (STAT-1) gene knockout mice exhibited hematopoietic cell tropism (macrophages and dendritic cells) and systemic disease development in response to murine NoV-1 infection. Clinical symptoms range from pneumonia and inflamed liver to inflammation in the brain and brain capillaries (Wobus et al. 2004; Scipioni et al. 2008; Karst et al. 2015). Moreover, it is still unknown whether the murine NoVs virus is a potent gut infectious agent of this particular vertebrate (Hsu et al. 2005).

Zoonotic Transmission of Norovirus and One Health Importance

Norovirus is an RNA virus, and many RNA viruses that affect people can also infect other vertebrate hosts in addition to humans because these are zoonotic. Many of those not considered zoonotic is thought to have recently evolved from zoonotic origins in evolutionary terms. Therefore, in the context of one health, norovirus is of particular importance. Man and animal's noroviruses genome has close similarities as well as the advent of recombinant NoV strains in various hosts have been demonstrated by research studies at micro level of environmental and genetic risk factors of noroviruses (Koopmans 2008). Bovine, porcine, canine, and feline genotypes contain the recombinants. It is conceivable that human-animal norovirus recombinants could form, particularly when comparing closely related animal and human genotypes. Multiple genotypes and genogroups of humans and animals can coexist in water, food sources, and filter-feeding shellfish, creating a potential source of co-infection in both species (Villabruna et al. 2019).

Veterinary professionals and the general public have both assessed positive in serological studies for immunoglobins against human NoV (Widdowson et al. 2005; Menon et al. 2013) and immunoglobulins against animal NoV (Farkas et al. 2005). Additionally, molecular research found human Nov. Strains in raw pork meat, cattle, and pig feces, and the most common strain found recently is more prevalent (GII.4) (Mattison et al. 2007). Furthermore, infection of gnotobiotic calves and piglets with man NoV demonstrated virus duplication and primary-infection (Cheetham et al. 2006; Souza et al. 2008).

This theory has not been proved yet, despite the likelihood that zoonotic transmission exists. More research is required to fully understand the significance of animals serving as reservoirs for human NoV infection because noroviruses are believed to be specifically oriented pathogens to particular vertebrates (Karst et al. 2015).

Diagnosis

Electron microscopy (EM) and real-time polymerase chain reaction (RT-PCR) are two methods used for the sensing of both human and animal NoVs. For the recognition of human(Vinjé 2015), swine (Machnowska et al. 2014) and bovine NoV strains (Jor et al. 2010, Yilmaz et al. 2011) other methods for RT- quantitative (RT-q PCR)-based Nov RNA detection and quantification have been reported. Immunoassays, like the enzyme-linked immunosorbent assay (ELISA), can identify viral foreign bodies or antibodies, both of which are the methods used to create recombinant virus-like particles (Wang et al. 2007; Mauroy et al. 2009.). For the virus diagnosis, other methods can also be used, including immunohistochemistry (Otto et al. 2011) and microarray hybridization (Wang et al. 2007; Scheuer et al. 2013).

The benefits and drawbacks of the methods used for the recognition of NoV infection are shown in the Table 1:

Control Strategies by Considering One Health Approach

The most common symptom of NoV infection in livestock animals is mild to moderate non-hemorrhagic diarrhea. Even when diarrhea has stopped, and animals are exhibiting the signs, the NoV fecal shedding can persist. In this situation, it is important to pay closer attention to the management of the environment and livestock to treat the afflicted animals clinically (O'Brien and Xagoraraki 2019).

Animals in the herd that have a NoV infection and are suspected or proven should be kept apart from the others. The key to managing NoV-induced diarrhea, which is typically a self-recovery infection that clears up within days of exposure, is to replace and maintain adequate levels of fluid and electrolytes. For calves, compared to piglets, fluid therapies are simpler to implement. Piglets may take oral medications designed to restore the hydro electrolytic balance. The use of broad-spectrum antibiotic therapy is advised in cases of severe diarrhea to control secondary infections. Milk after calving that contains maternal antibodies are likely to prevent infection and damage in nursing piglets' guts. Consuming colostrum may have some effect on the bovine NoV infection, even if it does not prevent it, by limiting the spread of infection and lowering the intensity and length of the diarrhea (Otto et al. 2011). To assess the impact of milk after calving on the development of the bovine and swine NoV infections, additional pathogenic studies should be carried out in the field.

Since noroviruses are very enduring in the environment, the development of appropriate science-based risk management policies that adhere to transboundary regulations is thus one of the most crucial factors in the control of norovirus at the interface between humans, animals, and the environment. The FAO, WHO, and OIE have made efforts to incorporate the One Health approach into their tripartite initiative's guiding principles, working closely with academic institutions, intergovernmental institutions, the private sector, nongovernmental organizations, public sectors, and other investors. The effective prevention and control of zoonotic diseases must start with an effective surveillance system, which includes a strong laboratory network. Revaluating the structure, resource allocation, and management of current systems is necessary in order to create a successful One Health implementation plan for boosting capacity at the national, regional, or international levels. Synergies between the human health, animal health, and ecosystem sectors can be developed and sustained with the help of these analyses (Gebreyes et al. 2014).

Prophylactic Measures

Animal infections are not preventable by vaccines. As a result, taking prophylactic measures is essential to prevent the disease. NoV infection and persistence in the environment should be controlled and/or prevented by removing waste, maintaining clean facilities, disinfecting, and taking other sanitary precautions. Since NoV is a waterborne pathogen, appropriate water management procedures should be used. This includes ensuring that the drinking water provided to the animals is of high quality, spotless, and has received an adequate amount of chlorine treatment. Given that NoVs are thought to be potentially zoonotic, public health-oriented management should also be taken into consideration. NoV is enduring in the surroundings and, depending on the circumstances, may not be inactivated by specific drug-oriented substances and heat. The effects of freezing and thawing do not seem to affect NoV (Nims and Plavsic 2013). Heat can reduce the infectivity of NoV by inactivating it, but extensive inactivation requires exposure times of at least 30 minutes and temperatures greater than 56°C (Duizer et al. 2004, Nims and Plavsic 2013). Irrespective of the calicivirus species or strain, higher temperatures (60°C) result in more thorough and consistent inactivation (Nims and Plavsic 2013). Because livestock manure has the potential to be a biofertilizer, it is applied to field land across the world to improve agriculture. Therefore, to lessen the spread of NoV in animal waste and to reduce the spread of manure-borne fecal contamination of the environment; an anaerobic bio-digester system is a tool that can be used to treat livestock

Table 1: Benefits and drawbacks of various diagnostic methods used for detection of NoV infection (Zaczek-Moczydlowska MA et al. 2021)

Diagnostic tests	Benefits	Drawbacks
Electron microscopy	Being able to recognize various virus pathogens	Low-sensitivity (limit of detection: 106 enteric virus particles per milliliter of fecal sample), lacking the ability to distinguish NoV from other small round enteric viruses, need qualified experts, costly equipment that is not frequently found in microbiological labs, time-consuming.
NGS	Extremely sensitive. Specificity is remarkably high. Virus detection and description in a single assay. Detection of microbial content in a single test. It may help to identify the infectious agent causing unexplained cases of suspected viral gut ailments.	Veterinary diagnostic labs lack access to costly equipment. Needs competent and skilled personnel.
Enzyme immunoassays	Ability to recognize soluble antigens as well as viral particles. A direct ELISA was demonstrated to be a pinpoint appropriate method (limit of sensing and 0.025ng of capsid protein viral antigen diluted 1:10,000 times within the fecal samples). Valuable for quickly screening more than one sample.	High specificity in VLP-based EIAs (underestimation of results may result from antigenically distinct NoV strains in circulation). Pig NoV VLP-based antibody ELISA shows a reaction with human NoV antibodies.
RT-q PCR	An improvement in sensitivity and specificity, even when compared to traditional RT-PCR assays. Eliminate the need for agar rose gel or hybridization analyses. Reduced sample carrying (lower risk of cross-contamination). Permit the measurement of the quantity of virus nucleic acid on a sample. Swift test.	There is a need for RT-q PCR equipment. The materials are costly. Virus genotyping is not possible with this method.

manure in order to provide safe bio-fertilizers, even though it is unclear whether gut viruses are effectively inactivated by anaerobic bio-digestion (Otto et al. 2011).

Conclusion

Bovine noroviruses are frequently found in cattle and occasionally at high frequency in cases of diarrhea in various countries, despite the fact that they have been studied much less than other viruses that are known to be the cause of NCD (neonatal calf diarrhea), such as rotavirus and coronavirus. The development of appropriate science-based risk management policies that adhere to transboundary regulations is thus one of the most crucial factors in the control of norovirus at the interface between humans, animals, and the environment. Animals in the herd that have a NoV infection and are suspected or proven should be kept apart from the others. The key to manage NoV-induced diarrhea, which is typically a self-recovery infection that clears up within days of exposure, is to replace and maintain adequate levels of fluid and electrolytes. The effective prevention and control of zoonotic diseases must start with an effective surveillance system, which includes a strong laboratory network. Revaluating the structure, resource allocation, and management of current systems is necessary in order to create a successful One Health implementation plan for boosting capacity at the national, regional, or international levels.

REFERENCES

Castells M et al., 2020. Detection, risk factors and molecular diversity of norovirus GIII in cattle in Uruguay. Infection, Genetics and Evolution 86: 104613. doi:https://doi.org/10.1016/j.meegid.2020.104613

Caul EOJJOCP, 1996. Viral gastroenteritis: small round structured viruses, caliciviruses and astroviruses. Part I. The Clinical and Diagnostic Perspective 49(11): 874.

Cheetham S et al., 2006. Pathogenesis of a genogroup II human norovirus in gnotobiotic pigs. Journal of virology 80: 10372-10381.

Duizer E et al., 2004. Inactivation of caliciviruses. Applied and Environmental Microbiology 70: 4538-4543.

Farkas T et al., 2005. Seroprevalence of noroviruses in swine. Journal of Clinical Microbiology 43: 657-661.

Frange P et al., 2012. Prevalence and Clinical Impact of Norovirus Fecal Shedding in Children with Inherited Immune Deficiencies. The Journal of Infectious Diseases 206(8): 1269-1274.

Gebreyes WA et al., 2014. The global one health paradigm: challenges and opportunities for tackling infectious diseases at the human, animal, and environment interface in low-resource settings. PLoS Neglected Tropical Diseases 8(11): e3257.

Hall G et al., 1984. Lesions of gnotobiotic calves experimentally infected with a calicivirus-like (Newbury) agent. Veterinary Pathology 21: 208-215.

Hsu CC et al., 2005. Development of a microsphere-based serologic multiplexed fluorescent immunoassay and a reverse transcriptase PCR assay to detect murine norovirus 1 infection in mice. Clinical and Vaccine Immunology 12: 1145-1151.

Jor E et al., 2010. SYBR Green based real-time RT-PCR assay for detection and genotype prediction of bovine noroviruses and assessment of clinical significance in Norway. Journal of Virological Methods 169: 1-7.

Jung K et al., 2014. Pathogenesis of GIII. 2 bovine norovirus, CV186-OH/00/US strain in gnotobiotic calves. Veterinary Microbiology 168: 202-207.

Karst SM et al., 2015. The molecular pathology of noroviruses. The Journal of Pathology 235: 206-216.

Machnowska P et al., 2014. Detection and characterization of potentially zoonotic viruses in faeces of pigs at slaughter in Germany. Veterinary Microbiology 168: 60-68.

Matthews JE et al., 2012. The epidemiology of published norovirus outbreaks: a review of risk factors associated with attack rate and genogroup. Epidemiology and Infection 140): 1161-1172.

Mattison K et al., 2007. Human noroviruses in swine and cattle. Emerging Infectious Diseases: 13: 1184.

Mauroy A et al., 2009. Epidemiological study of bovine norovirus infection by RT-PCR and a VLP-based antibody ELISA. Veterinary Microbiology 137: 243-251.

Menon VK et al., 2013. Exposure to human and bovine noroviruses in a birth cohort in southern India from 2002 to 2006. Journal of Clinical Microbiology 51: 2391-2395.

Nims R and Plavsic M, 2013. Inactivation of caliciviruses. Pharmaceuticals 6: 358-392.

Otto PH et al., 2011. Infection of calves with bovine norovirus GIII. 1 strain Jena virus: an experimental model to study the pathogenesis of norovirus infection. Journal of Virology 85: 12013-12021.

O'Brien E and Xagoraraki I, 2019. A water-focused one-health approach for early detection and prevention of viral outbreaks. One Health 7: 100094.

Patel MM et al., 2008. Systematic literature review of role of noroviruses in sporadic gastroenteritis. Emerging Infectious Diseases 14(8): 1224-1231.

Scheuer KA et al., 2013. Prevalence of porcine noroviruses, molecular characterization of emerging porcine sapoviruses from finisher swine in the United States, and unified classification scheme for sapoviruses. Journal of Clinical Microbiology 51: 2344-2353.

Scipioni A et al., 2008. Animal noroviruses. The Veterinary Journal 178: 32-45.

Shen Q et al., 2012. Recombinant porcine norovirus identified from piglet with diarrhea. BMC Veterinary Research 8: 1-6.

Siebenga JJ et al., 2009. Norovirus illness is a global problem: emergence and spread of norovirus GII. 4 variants, 2001–2007. The Journal of Infectious Diseases 200(5): 802-812.

Souza M et al., 2008. Pathogenesis and immune responses in gnotobiotic calves after infection with the genogroup II. 4-HS66 strain of human norovirus. Journal of Virology 82: 1777-1786.

Villabruna N et al., 2019. Animals as reservoir for human norovirus. Viruses 11: 478.

Vinjé J, 2015. Advances in laboratory methods for detection and typing of norovirus. Journal of Clinical Microbiology 53: 373-381.

Wang QH et al., 2007. Porcine enteric caliciviruses: genetic and antigenic relatedness to human caliciviruses, diagnosis and epidemiology. Vaccine 25: 5453-5466.

Widdowson MA et al., 2005. Detection of serum antibodies to bovine norovirus in veterinarians and the general population in the Netherlands. Journal of Medical Virology 76: 119-128.

Wobus CE et al., 2004. Replication of Norovirus in cell culture reveals a tropism for dendritic cells and macrophages. PLoS Biology 2: e432.

Yilmaz H et al., 2011. First report on the phylogeny of bovine norovirus in Turkey. Archives of Virology 156: 143-147.

Zika Virus: A Pathological and Clinical Perspective

AUTHORS DETAIL

Muhammad Imran[1*], Munazza Aslam[1], Muhammad Kashif Saleemi[1], Shengbo Cao[2], Jing Ye[2], Al-Hafiza Shafia Tehseen Gul[1], Aisha Khatoon[1], Muhammad Wasim Usmani[1,3], Mughees Aizaz Alvi[4], Shah Nawaz[5], Muhammad Imran[6], Muhammad Ahsan Naeem[7] and Maria Jamil[1]

[1]Department of Pathology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[2]State Key Laboratory of Agricultural Microbiology, Huazhong Agricultural University, Wuhan, Hubei, China
[3]Faculty of Veterinary & Animal Sciences Ziauddin University, Karachi
[4]Department of Clinical Medicine and Surgery, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[5]Department of Anatomy, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[6]Department of Parasitology, Faculty of Veterinary Science, University of Agriculture, Faisalabad, Pakistan
[7]Department of Basic Sciences, KBCMA College of Veterinary and Animal Sciences, Narowal, Pakistan
*Corresponding author: dr.mimran@uaf.edu.pk

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INTRODUCTION

There are certain viruses that are of public health concern and pose an alarming situation upon their spread. Arboviruses (arthropod-borne viruses) are considered as one of those viruses (Girard et al. 2020). They are transmitted between vertebrate hosts and vectors. Arboviruses belong to one of three families known as *Flaviviridae*, *Togaviridae* and *Bunyaviridae*. Flaviviruses are important pathogens that can re-emerge on regular basis, having serious health risk, and affect millions of people worldwide annually (Laureti et al. 2018). The *Flaviviridae* is a large family, contains four distinct genera: *Hepacivirus*, *Pestivirus*, *Pegivirus*, and *Flavivirus* (Gubler 2002). Among these four genera, *Flavivirus* is the largest one, consists of more than 70 viruses, and is found in every continent except Antarctica (Leyssen et al. 2000).

Based upon phylogenetic analysis and ecological niches, *Flaviviruses* are comprised of four major groups i.e., Tick-borne, mosquito-borne, insect-specific, and no known vector flaviviruses (Junglen et al. 2009). Among these four groups, most members fall in the vector-borne category of flaviviruses, spread by ticks and mosquitoes to susceptible vertebrates. Zika virus (ZIKV) is an important member of mosquito-borne *flavivirus* that is closely related to Dengue virus (DENV), Yellow fever virus (YFV), Japanese encephalitis virus (JEV), West Nile virus (WNV), and tick-borne encephalitis virus (TBEV). These arthropod-transmitted viruses are the global threat to human health (Gwon et al. 2020; Pierson et al. 2020).

Clinical manifestations of flaviviruses are variable from mild temperature to serious hemorrhagic and menengioencephalitis conditions. For example, ZIKV, JEV, WNV, and TBEV, are neurotropic and can spread to the brain and spinal cord, and cause encephalitis, meningitis, and acute flaccid paralysis while YFV and DENV are viscerotropic, and cause hepatic damage, vascular leakage, and hemorrhagic fever. Uniquely, ZIKV can also transmit sexually and affects both neonates and adults, and causes microcephaly and Guillain-Barré syndrome (GBS) respectively (Daep et al. 2014; Pierson et al. 2020).

The World Health Organization (WHO) categorized the ZIKV infection as a public health emergency of global concern in February 2016 as a result of the virus's rapid spread throughout the Americas (Petersen et al. 2016).

History and Epidemiology

In 1947, Zika virus was discovered during a study of yellow fever in the forest of Zika, Uganda (Dick 1953). Febrile sentinel rhesus macaque monkey was the source by which the virus was isolated. These monkeys were kept there for the purpose of course surveillance of yellow fever. Mosquito population of *Aedes* (*A.*) *africanus* of the same forest was also harboring the ZIKV (Haddow et al. 2013). Upon its discovery from the mosquito, it was recognized that the mosquito was responsible for the spread of ZIKV. Numerous studies further clarified the species of mosquitoes that were involved in the spread of this virus. In 1954, three ZIKV cases in human were first detected in Nigeria (Macnamara 1954). ZIKV was reported globally especially in Africa, Asia, and Oceania, according to sero-surveillance investigations in people. Individuals were not clinically ill, but antibodies against the ZIKV were detected in the blood (Hayes 2009). Serological diagnosis of ZIKV infection is challenging due to high cross-reactivity among other flaviviruses and it ultimately leads to increased prevalence

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(Marbán-Castro et al. 2021). Historically, only few ZIKV-infected patients were found based on clinical manifestations. In 2007, the first outbreak of ZIKV was occurred in the Yap which is one of the Federated states of Micronesia (Dupont-Rouzeyrol et al. 2015). In this outbreak, out of 73% ZIKV infected population, 18% population showed clinical signs. Since then, the ZIKV infection has been rapidly spreading to other parts of the world like French Polynesia, Easter Island, the Cook Islands, New Caledonia, and most recently America. This part of world has been experienced the expansion of ZIKV in the early 2010 (Imperato 2016). Most of the ZIKV-infected patients in these regions showed similar neurological complications like GBS to that of the Yap outbreak (Carod-Artal 2018). GBS is an autoimmune disorder that affects the peripheral nervous system (PNS), resulted in numbness and tingling, however paralysis may occur in severe cases (Dimachkie et al. 2013). All type of ZIKV infections eventually lead to the paralysis. In French, Polynesia GBS incidence was increased up to 20 folds (Tappe et al. 2015).

The first autochthonous ZIKV infection was discovered at the beginning of 2015 in northeastern Brazil (Zanluca et al. 2015). About 14 Brazilian states experienced an increase in ZIKV activity during same year. The estimated cases of ZIKV were between 440,000 to 1,300,000. In 2015, It was surprising to see an increased number of ZIKV-associated microcephaly cases in Brazil (Alvarado et al. 2017). More than 4000 cases of probable microcephaly had also been reported by February 2016. Although it's possible that some of these cases were overreported or misdiagnosed. Retrospective research in French Polynesia supported this conclusion, showing increased microcephaly and prenatal abnormalities (Cauchemez et al. 2016).

In October 2015, the first ZIKV transmission was reported in Colombia and about 51,473 ZIKV suspected cases were recorded by March 2016, with 2090 of those cases being confirmed in labs. Since ZIKV first case in Brazil, spread alarmingly to South and Central America as well as the Caribbean countries. From February to November 2016, WHO declared ZIKV as a public health emergency due to increased cases of microcephalic in infants. ZIKV autochthonously transmitted by mosquitoes has also been recorded in 48 nations and territories of the America (Song et al. 2017).

Additionally, incidents of sexually transmitted ZIKV cases have been documented in the US, Argentina, Chile, Canada, and Peru. With the exception of Mexico, Panama, Turks and Caicos Islands, every ZIKV-affected country and territory in the American subcontinent had seen a decline in ZIKV cases by November 2016 (Gao et al. 2016). Till now, a total of 20 countries and territories in the America have recorded 2311 confirmed cases of ZIKV-associated congenital syndrome. There were 4444 confirmed ZIKV cases reported to ArboNET in US states and federal districts; out of these, 36 cases were sexually transmitted across the country, and 182 cases were locally acquired mosquito-borne cases in Florida, where autochthonous transmission was initially noted in July 2016 and is still present in the Miami Beach area and the county of Miami-Dade. The US Zika Pregnancy Registry had received reports of 33 newborn babies and miscarriages that resulted in birth abnormalities (Reynolds et al. 2017).

Transmission

The infected mosquito plays the primary role in the transmission of ZIKV to humans (Maxian et al. 2017). There are several other means by which virus transmission has been reported from mother to child via pregnancy and breastfeeding. ZIKV can be transferred by blood transfusion and sexual contact (Fig. 1). Control strategies against ZIKV are difficult to develop as there are several modes of transmission (Rather et al. 2017). Approximately 80% cases of ZIKV infection are asymptomatic or having mild signs seen in affected patients. ZIKV is a mosquito-borne flavivirus having two distinct transmission cycles (Huang et al. 2019). The first one is the sylvatic cycle during which ZIKV transmission occurs between non-human primates (monkeys) and mosquitoes. The second transmission cycle is the urban cycle during which this virus circulates between people and mosquitoes in urban areas (Weaver 2014). However, this virus can be transferred from non-human primates to humans by mosquitoes when they come into close contact. ZIKV has been isolated from several different *Aedes* mosquito species in Africa and Asia, including *Aedes aegypti (A. aegypti), A. albopictus, A. africanus, A. luteocephalus, A. furcifer, A. vittatus, and A. opok* which may serve as vectors for virus transmission in specific endemic locations (Ayres 2016). Moreover, *A. hensilli* and *A. polynesiensis* were both proposed as potential vectors for the epidemics in Yap and French Polynesia, respectively (Richard et al. 2016). It has been reported that vector competency of different mosquitoes in YFV and DENV is based on population density of the mosquitos in a certain habitat of an area and genetic variability of both virus and vector. This observation is probably accurate for ZIKV as well (Valderrama et al. 2017).

Although in urban cycle, *A. aegypti* and *A. albopictus* are the predominant species for ZIKV transmission, but vector competency of *A. aegypti* is more than *A. albopictus* because of its more anthropophilic nature and this specie can infect many people with a single blood meal. Both these mosquito species are active in day light and widely present in tropical and subtropical countries (Maxian et al. 2017).

Pathogenesis

When a mosquito carrying ZIKV, bites a human, it spreads the virus via blood streams to various body tissues and multiplies in the dendritic cells (Guarner et al. 2019). This virus often produces a self-limiting infection, However pregnant females may have teratogenic effects.

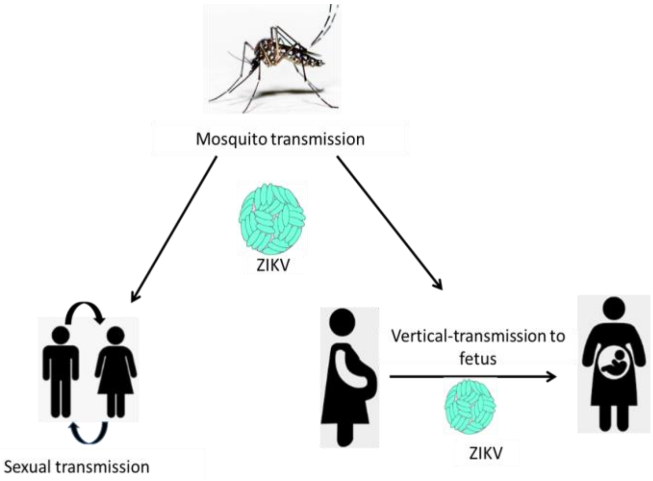

Fig. 1: ZIKV transmission in human

The ZIKV replicates in fetal brain and develops escalating effects during the first trimester of pregnancy and this infection lasts longer in pregnant women (Bălălău et al. 2020). In ZIKV infection, the carrier mosquito bites to host leading initial replication of virus in Langerhans cells followed by regional lymph node. Afterward, through the hematogenous route, this virus spreads to target tissues (Muffat et al. 2018).

ZIKV mainly infects and replicates in neuronal progenitor cells (NPCs) through interacting with different types of receptors (AXL, DC-SIGN, TAM, TIM, AXL and TYRO 3) which ultimately impairs fetal brain and causes microcephaly and other neuronal disorder (Muffat et al. 2018).

The mechanism of genome replication in mosquito-borne flaviviruses is of great importance in vaccine development and treatment purposes (Taylor et al. 2015). *Flavivirus* entry in the host cells depends upon the contact of E protein with cognate receptors (Slon Campos et al. 2018). The structural heterogeneity of flaviviruses virion may increase the range of tissue infectivity both in vertebrate and non-vertebrate hosts (Laureti et al. 2018). There are three ectodomains of the E protein (EDI, EDII, and EDIII) in flaviviruses. For viral entry, the third ectodomain EDIII interacts with glycosaminoglycan attachment factor, followed by high-affinity receptor binding, and then it leads to clatherin-dependent endocytosis. Afterward, transportation occurs to endosomes, where the acidic milieu stimulates changes in the conformation of E protein which ultimately leads to fusion of virus to host cell membrane (Smit et al. 2011).

Following the fusion of virus and endosomal membrane, viral genome is translated to a polyprotein precursor that gives rise to structural and NS proteins (Stiasny et al. 2011). Assembly of immature virus particles occurs in the endoplasmic reticulum (ER). These immature virions are non-infectious having an uncleaved precursor membrane (prM) with E protein. Maturation occurs after trafficking in the Trans-Glogi network (TGN) by host protease, called furin (Zhang et al. 2003). In flaviviruses, R-X-R/K-R is a specific sequence that is recognized by furin and converts PrM to M in the acidic condition of TGN which ultimately lead to flavivirus maturation. Afterward, these mature and infectious virions are exocytosed in the extracellular compartment. For flavivirus maturation, this furin-dependent proteolytic cleavage is a critical stage that could be targeted to debilitate virus pathogenicity and infectivity (Smed-Sörensen et al. 2018).

Basically, different flaviviruses attach to various receptors for entrance and the experimental research has shown that knocking off receptors does not completely protect against viral infection. AXL, an important host receptor for ZIKV replication. This AXL receptor is overexpressed in glial cells and substantially expresses throughout neurogenesis in the development of the human cortex. Studies have reported that deletion of AXL does not impair the ZIKV infectivity to NPCs. According to a study, the TAM receptors were shown to be unnecessary for ZIKV infection (Hastings et al. 2017). These studies generally indicate that extravagant entry receptors exist for ZIKV infection (Valdés López et al. 2019).

Genome Organization and Role of Viral Proteins in Pathogenesis

ZIKV is an icosahedral, enveloped, and positive-strand RNA virus. In one open reading frame (ORF), approximately 11 kb genome is translated into a precursor polyprotein with 3.4 k amino acids. In addition, these amino acids then co- and post-translated by ZIKV and host enzymes into structural (S) and non-structural (NS) proteins. Core (C), membrane (M), and envelope (E) are structural proteins, whereas NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are non-structural proteins. (Imran et al. 2019).

The ZIKV life cycle includes these seven NS proteins in distinct stages. However, these S proteins are necessary for host immunity and virus replication. Antibodies specifically target glycoprotein E because it makes it easier for viruses to enter their host. ZIKV controls the antibody response by changing the amino acids around the Asn154 glycosylation site in the viral E protein (Long et al. 2019). ZIKV is able to mediate the antibody response. This suggests that glycosylation is a key component of virus morphology and tropism as well as its pathogenesis and immune system evasion. It is still unclear what are the main functions of PrM and capsid during ZIKV pathogenesis. It has been reported that capsid plays an important role in virus assembly. A conserved portion of PrM protein is responsible for viral maturation, egress, and secretion. Therefore, preventing PrM from its functioning will prevent viral pathogenicity and infection (Imran et al. 2019).

The NS1 is thought to be required in later steps of virus replication through evading the immune response. NS2B-NS3 is involved in proteolytic processing of the viral polyprotein and has been considered as a promising therapeutic target. NS3 also functions as RNA helicase,

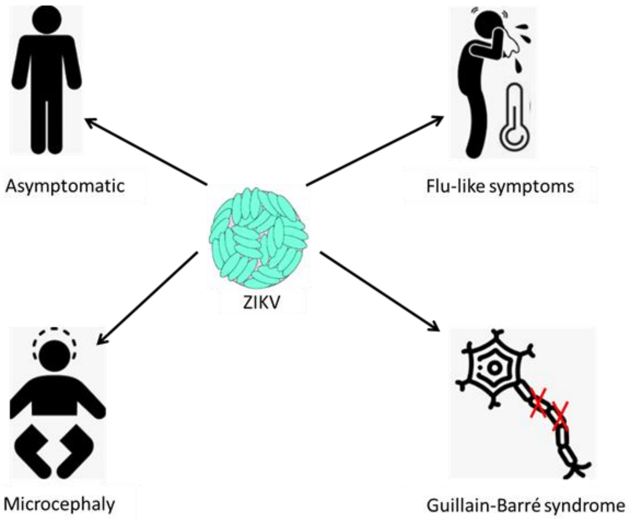

Fig. 2: Clinical manifestations of ZIKV

which facilitates replication of the viral genome. NS4A and NS4B interactions are also essential for viral replication by modulating the innate immune response. NS5 has RNA-dependent RNA polymerase, RNA guanylyltransferase and methyltransferase activity, required in the final step of generating genomic 5´ cap (Kang et al. 2017).

Clinical Presentation

In most cases of ZIKV, there are mild clinical signs. The initial symptoms include fever, body aches, rash on the skin, and headache. As the clinical manifestations are misinterpreted for influenza, there is an underreporting of ZIKV infections (Saiz et al. 2016). The symptoms include diarrhea, retro-orbital discomfort, lymphadenopathy, and edema. ZIKV infection is underreported because of signs and symptoms including arthralgia, maculopapular rash, and conjunctivitis that are consistent with dengue fever illness (Moghadam et al. 2016). Patients with ZIKV can also have malaise, dizziness, stomachache, hematospermia, anorexia, dizziness, prostatitis, and lightheadedness (Shapshak et al. 2015).

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is an autoimmune disorder in which the immune system of the patient harms the nerve cells, resulting in muscle weakness and, in some cases, paralysis. Recently, GBS cases have been increased in several countries that have had ZIKV infections (Fig. 2). The arms and legs can become weak, and in more serious cases, the breathing muscles can also be affected by GBS symptoms. These signs may last for weeks or months. The majority of GBS patients get complete recovery, while some have a lifelong impairment. GBS causes very few fatalities (Goodyear et al. 1999; Mier-y-Teran-Romero et al. 2018).

Prior to the Yap Island epidemic, ZIKV infection was thought to be self-limited; nevertheless, following the 2013 French Polynesia outbreak, an extraordinary rise in the prevalence of acquired neurological diseases, including GBS, was seen (Styczynski et al. 2017). A French Polynesian female, who experienced flu-like symptoms seven days before developing GBS in November 2013, was the first patient with GBS linked to ZIKV infection. During the outbreak in French Polynesia between October 2013 and April 2014, 42 people were diagnosed with GBS, according to a single-center investigation (Baskar et al. 2018). During the outbreak in French Polynesia, this severe neurological consequence was first recognized as being linked to ZIKV infection (Cao-Lormeau et al. 2016). Other arboviruses like DENV, WNV, JEV, and CHIKV had also been reported occasionally to induce GBS. The increase in the occurrence of ZIKV and GBS was at the same time, and DENV serotypes 1 and 3 were also circulating at the same time, suggests a potential causative connection between these three infections. There is a possibility that contemporaneous or sequential ZIKV infection, with or without DENV infection, may be a risk factor for the emergence of GBS using two control series. However, the mechanism of Guillain-Barré syndrome, which results in temporary paralysis, is unknown, there is growing clinical evidence that the ZIKV may have a role in the development of GBS (Hughes et al. 2005; Rahimi 2020).

Microcephaly

Microcephaly is a neurological disorder in which a baby's brain does not develop normally, resulting in a smaller-than-normal head (Fig. 2). The condition can be classified into two categories: (1) congenital (primary) microcephaly, which manifests during pregnancy or at birth, and (2) postnatal (secondary) microcephaly, which appears post-delivery. In contrast to secondary microcephaly, this is thought to be developed by decrease in number of dendritic processes and synaptic connections. The congenital microcephaly is usually accompanied by a reduction in the number of neurons produced during the neurogenesis (Abuelo 2007).

A change in the DNA sequence (genetic mutations), peri- and postnatal brain damage, prenatal infections, and teratogenic substances can result in microcephaly. Congenital microcephaly had previously been linked to the cytomegalovirus and rubella viruses (Hanshaw 1971). The incidence of babies with microcephaly started to increase in September 2015; as a result, about 8301 cases were registered in Brazil from November 2015 to July 2016 which showed a casual association between microcephaly and prenatal problems for ZIKV. Consequently, one prospective study and two retrospective studies from Brazil and French Polynesia respectively have revealed that ZIKV infection may increase the risk of microcephaly (de Magalhães-Barbosa et al. 2016).

Congenital microcephaly is defined as a baby having a head circumference (HC) below the 3rd percentile of age and sex at birth for live babies. In general, HC has been observed to assess brain size and growth and is a reliable indicator of total brain volume. Brain size variation is a significant risk factor for motor and cognitive disorders (de Araújo et al. 2016). According to data gathered on pre- and post-natal clinical cases, ZIKV infection during pregnancy is linked to microcephaly and other deformities including facial disproportionality, hypertonia/ spasticity, cutis girata, and hyperreflexia, and is sporadically accompanied by neuroimaging abnormalities like calcifications, lissencephaly, and ventriculomegaly. Recently, a preliminary result of the first case control research demonstrated that 13 out of 32 babies with microcephaly and none of the 62 controls without microcephaly had ZIKV infection, confirmed through laboratory and validated the link between ZIKV and microcephaly. Additionally, it has been speculated that congenital ZIKV infection is linked to ocular and hearing defects in children (de Carvalho Leal et al. 2019).

Other Neurological Complications Associated with ZIKV

Recently, case studies like those of an 81-year-old man and a 15-year-old girl diagnosed with meningoencephalitis and acute myelitis respectively described the ZIKV infection association with additional neurological issues. Future study is likely to reveal both these neurological and non-neurological adverse effects produced by ZIKV infection (Calvet et al. 2016). To further understand the potential contribution of ZIKV infection in adults and children, case-control or cohort studies will be necessary in addition to well-described case reports.

Control Strategies

Despite licensed vaccine availability, a still high number of cases were reported over the year, highlighting the need for specific antiviral therapies to limit the flaviviruses infections. Several antiviral drugs have been investigated to assess anti-flaviviral activity, but due to high mutation rates, flaviviruses often escape from viral proteins targeted antiviral drugs. To overcome this lack of treatment options against flaviviruses, a host targeted drug could represent a better antiviral approach (Imran et al. 2022a). In these situations, and to address the issue at large, adequate mechanical, chemical, biological, and genetic control techniques must be strengthened in order to manage mosquito populations. In addition, a number of other known ZIKV transmission routes that have recently become more significant, including intrauterine, sexual, and blood-borne spread, need to be checked and kept under control by taking the proper precautions and exercising the utmost caution during sexual activity, blood transfusion, and organ transplantation. Pasteurization, detergents, chemicals, and filtration can lower the viral load effectively in medicinal products made from plasma. In addition, improving ZIKV surveillance and monitoring, as well as limiting travel to Zika-infected areas, would help to keep the virus infection under control (Imran et al. 2022b).

Conclusion

WHO declared the ZIKV global outbreak as a Public Health Emergency of International Concern in 2016. ZIKV and the related neurological consequences pose a long-term global threat to public health, as demonstrated by the overwhelming experience of the previous few years. ZIKV infection does not pose a significant threat to infected adults. However, its risk is more during pregnancy causing fetal abnormalities. This is in contrast to other "newly emerging" infections that can cause severe morbidity and mortality in infected adults or pediatric hosts. In order to control any potential ZIKV-related epidemic in various countries, it is essential to raise the level of awareness among health professionals and to make necessary changes regarding improvements in vector control and disease surveillance systems.

REFERENCES

Abuelo D, 2007. Microcephaly syndromes. Seminars in pediatric neurology 14: 118-127.

Alvarado MG et al., 2017. Zika virus infection in pregnancy, microcephaly, and maternal and fetal health: what we think, what we know, and what we think we know. Archives of Pathology and Laboratory Medicine 141: 26-32.

Ayres CF, 2016. Identification of Zika virus vectors and implications for control. The Lancet Infectious Diseases 16: 278-279.

Bălălău OD et al., 2020. Maternal infections with an increased risk of transmission to the foetus; a literature review. Journal of Clinical and Investigative Surgery 5: 66-72.

Baskar D et al., 2018. Antibodies to Zika virus, Campylobacter jejuni and gangliosides in Guillain–Barre syndrome: A prospective single-center study from southern India. Neurology India 66: 1324.

Calvet GA et al., 2016. Zika virus infection: epidemiology, clinical manifestations and diagnosis. Current opinion in infectious diseases 29: 459-466.

Cao-Lormeau VM et al., 2016. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. The Lancet 387: 1531-1539.

Carod-Artal FJ, 2018. Neurological complications of Zika virus infection. Expert Review of Anti-Infective Therapy 16: 399-410.

Cauchemez S et al., 2016. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. The Lancet 387: 2125-2132.

Daep CA et al., 2014. Flaviviruses, an expanding threat in public health: focus on dengue, West Nile, and Japanese encephalitis virus. Journal of Neurovirology 20: 539-560.

de Araújo TVB et al., 2016. Association between Zika virus infection and microcephaly in Brazil, January to May 2016: preliminary report of a case-control study. The Lancet Infectious Diseases 16: 1356-1363.

de Carvalho Leal M et al., 2019. Hearing loss from congenital Zika virus infection. Topics in Magnetic Resonance Imaging 28: 19-22.

de Magalhães-Barbosa MC et al., 2016. Trends of the microcephaly and Zika virus outbreak in Brazil, January–July 2016. Travel Medicine and Infectious Disease 14: 458-463.

Dick GW, 1953. Epidemiological notes on some viruses isolated in Uganda (Yellow fever, Rift Valley fever, Bwamba fever, West Nile, Mengo, Semlik-forest, Bunyamwera, Ntaya, Uganda S and Zika viruses). Transactions of the Royal Society of Tropical Medicine and Hygiene 47: 13-48.

Dimachkie MM et al., 2013. Guillain-Barré syndrome and variants. Neurologic Clinics 31: 491-510.

Dupont-Rouzeyrol M et al., 2015. Co-infection with Zika and dengue viruses in 2 patients, New Caledonia, 2014. Emerging Infectious Diseases 21: 381.

Gao D et al., 2016. Prevention and control of Zika as a mosquito-borne and sexually transmitted disease: a mathematical modeling analysis. Scientific Reports 6: 1-10.

Girard M et al., 2020. Arboviruses: A global public health threat. Vaccine 24: 3989-3994.

Goodyear CS et al., 1999. Monoclonal antibodies raised against Guillain-Barré syndrome–associated Campylobacter jejuni lipopolysaccharides react with neuronal gangliosides and paralyze muscle-nerve preparations. The Journal of Clinical Investigation 104: 697-708.

Guarner J et al., 2019. Four human diseases with significant public health impact caused by mosquito-borne flaviviruses: West Nile, Zika, dengue and yellow fever. Seminars in diagnostic pathology 36: 170-176.

Gubler DJ, 2002. The global emergence/resurgence of arboviral diseases as public health problems. Archives of Medical Research 33: 330-342.

Gwon YD et al., 2020. Antiviral activity of Benzavir-2 against emerging flaviviruses. Viruses 12: 351.

Haddow AD et al., 2013. First isolation of Aedes flavivirus in the Western Hemisphere and evidence of vertical transmission in the mosquito Aedes (Stegomyia) albopictus (Diptera: Culicidae). Virology 440: 134-139.

Hanshaw JB, 1971. Congenital cytomegalovirus infection: a fifteen year perspective. The Journal of Infectious Diseases 123: 555-561.

Hastings et al., 2017. TAM receptors are not required for Zika virus infection in mice. Cell Reports 19: 558-568.

Hayes EB, 2009. Zika virus outside Africa. Emerging Infectious Diseases 15: 1347.

Huang YJS et al., 2019. Emergence and re-emergence of mosquito-borne arboviruses. Current Opinion in Virology 34: 104-109.

Hughes RAC et al., 2005. Guillain-barre syndrome. The Lancet 366: 1653-1666.

Imperato PJ, 2016. The convergence of a virus, mosquitoes, and human travel in globalizing the Zika epidemic. Journal of Community Health 41: 674-679.

Imran M et al., 2019. Decanoyl-arg-val-lys-arg-chloromethylketone: An antiviral compound that acts against flaviviruses through the inhibition of furin-mediated prm cleavage. Viruses 11: 1011.

Imran M et al., 2022a. Screening of novel synthetic derivatives of dehydroepiandrosterone for antivirals against flaviviruses infections. Virologica Sinica 37: 94-106.

Imran M et al., 2022b. Epidemiological trends of mosquito-borne viral diseases in Pakistan. Animal Diseases 2: 1-10.

Junglen S et al., 2009. A new flavivirus and a new vector: characterization of a novel flavivirus isolated from uranotaenia mosquitoes from a tropical rain forest. Journal of Virology 83: 4462-4468.

Kang C et al., 2017. Zika virus protease: an antiviral drug target. Trends in Microbiology 25: 797-808.

Laureti M et al., 2018. Flavivirus receptors: diversity, identity, and cell entry. Frontiers in Immunology 9: 2180.

Leyssen P et al., 2000. Perspectives for the treatment of infections with Flaviviridae. Clinical Microbiology Reviews 13: 67-82.

Long F et al., 2019. Structural basis of a potent human monoclonal antibody against Zika virus targeting a quaternary epitope. Proceedings of the National Academy of Sciences 116: 1591-1596.

Macnamara FN, 1954. Zika virus: a report on three cases of human infection during an epidemic of jaundice in Nigeria. Transactions of the Royal Society of Tropical Medicine and Hygiene 48: 139-145.

Marbán-Castro E et al., 2021. Zika virus infection in pregnant women and their children: A review. European Journal of Obstetrics and Gynecology and Reproductive Biology 265: 162-168.

Maxian O et al., 2017. Zika virus dynamics: When does sexual transmission matter? Epidemics 21: 48-55.

Mier-y-Teran-Romero L et al., 2018. Guillain–Barré syndrome risk among individuals infected with Zika virus: a multi-country assessment. BMC Medicine 16: 1-8.

Moghadam SRJ et al., 2016. Zika virus: A review of literature. Asian Pacific Journal of Tropical Biomedicine 6: 989-994.

Muffat J et al., 2018. Human induced pluripotent stem cell-derived glial cells and neural progenitors display divergent responses to Zika and dengue infections. Proceedings of the National Academy of Sciences 115: 7117-7122.

Petersen E et al., 2016. Rapid spread of Zika virus in the Americas-implications for public health preparedness for mass gatherings at the 2016 Brazil Olympic Games. International Journal of Infectious Diseases 44: 11-15.

Pierson TC et al., 2020. The continued threat of emerging flaviviruses. Nature Microbiology 5: 796-812.

Rahimi K, 2020. Guillain-Barre syndrome during COVID-19 pandemic: an overview of the reports. Neurological Sciences 41: 3149-3156.

Rather IA et al., 2017. Prevention and control strategies to counter ZIKA epidemic. Frontiers in Microbiology 8: 305.

Reynolds MR et al., 2017. Vital signs: update on Zika virus–associated birth defects and evaluation of all US infants with congenital Zika virus exposure—US Zika Pregnancy Registry, 2016. Morbidity and Mortality Weekly Report 66: 366.

Richard V et al., 2016. Vector competence of French Polynesian Aedes aegypti and Aedes polynesiensis for Zika virus. PLoS Neglected Tropical Diseases 10: 0005024.

Saiz JC et al., 2016. Zika virus: the latest newcomer. Frontiers in Microbiology 7: 496.

Shapshak P et al., 2015. Zika virus. In: Paul S, John TS, Charurut S, Jens H, editors. Global Virology I-Identifying and

Investigating Viral Diseases. Springer, New York, USA; pp: 477-500.

Slon Campos JL et al., 2018. The immune response against flaviviruses. Nature Immunology 19: 1189-1198.

Smed-Sörensen A et al., 2018. Emerging viruses: host immunity and novel therapeutic interventions. Frontiers in Immunology 9: 2828.

Smit JM et al., 2011. Flavivirus cell entry and membrane fusion. Viruses 3: 160-171.

Song BH et al., 2017. Zika virus: History, epidemiology, transmission, and clinical presentation. Journal of Neuroimmunology 15: 50-64.

Stiasny K et al., 2011. Molecular mechanisms of flavivirus membrane fusion. Amino acids 41: 1159-1163.

Styczynski AR et al., 2017. Increased rates of Guillain-Barré syndrome associated with Zika virus outbreak in the Salvador metropolitan area, Brazil. PLoS Neglected Tropical Diseases 11: 0005869.

Tappe D et al., 2015. Acute Zika virus infection after travel to Malaysian Borneo, September 2014. Emerging Infectious Diseases 21: 911.

Taylor A et al., 2015. Fc receptors in antibody-dependent enhancement of viral infections. Immunological Reviews 268: 340-364.

Valderrama A et al., 2017. Interaction of Flavivirus with their mosquito vectors and their impact on the human health in the Americas. Biochemical and Biophysical Research Communications 492: 541-547.

Valdés López JF et al., 2019. Chikungunya virus and Zika virus, two different viruses examined with a common aim: role of pattern recognition receptors on the inflammatory response. Journal of Interferon and Cytokine Research 39: 507-521.

Weaver SC, 2014. Arrival of chikungunya virus in the new world: prospects for spread and impact on public health. PLoS Neglected Tropical Disease 8: 2921.

Zanluca C et al., 2015. First report of autochthonous transmission of Zika virus in Brazil. Memórias do Instituto Oswaldo Cruz 110: 569-572.

Zhang Yet al., 2003. Structures of immature flavivirus particles. The EMBO Journal 22: 2604-2613

20

Lumpy Skin Disease

AUTHORS DETAIL

Muhammad Arif Zafar*, Adnan Hassan Tahir and Muhammad Farhan Rahim

Department of Clinical Studies, Faculty of Veterinary and Animal Sciences
Pir Mehr Ali Shah-Arid Agriculture University, 46300, Rawalpindi-Pakistan
*Corresponding author: dr.mazafar@uaar.edu.pk

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INTRODUCTION

Lumpy skin disease (LSD) is an economically important disease of large ruminants and considered as major threat to livestock farmers in Africa, Europe and Asia (Flannery et al. 2022; Wolff et al. 2022). The World Organization for Animal Health (WOAH; formerly OIE) declared it as transboundary and compulsory notifiable disease due to its rapid spread and significant economic losses in terms of poor hide or skin quality, reduction in milk production, abortion or infertility, poor growth rate and even death of animals (Anonymous 2021). The recent outbreak of LSD in naïve countries indicates the importance of control and eradication of the disease (Sprygin et al. 2019). The major symptoms of LSD are pyrexia or fever, nasal discharge, swelling of the lymph nodes, nodules or nodular lesions covering the skin of entire body, mucus membranes of respiratory and gastrointestinal track (Namazi and Tafti 2021).

The cattle are more affected than water buffaloes. Animal of any age, especially the young stock, and breed can be affected by this disease (Shen et al. 2011). Female cattle are more prone to the disease as compared to male because it is supposed that female cattle are exposed to many stress conditions such as pregnancy, parturition and less amount of feed given to high yielding animals compared to their actual requirements. There is an inverse relationship between lactation number and occurrence of LSD in cattle although researchers were unable to justify the possible reason behind this phenomena (Hasib et al. 2021). New animal's entry into farm may cause spread of disease. The LSD is transmitted mainly through vectors and mechanical means (Magori-Cohen et al. 2012; Paslaru et al. 2021).

Etiology

The LSD is a viral disease associated with Lumpy Skin Disease Virus (LSDV), a double-stranded DNA virus, belongs to genus Capripoxvirus, sub-family Chordopoxviridae and family Poxviridae. The LSDV is a large-sized and brick-shaped virion having 293-299 nm length and 262-273 nm width. This virus is closely related to the sheep and goat pox viruses (Constable et al. 2016; Givens 2018).

Epidemiology

Host Susceptibility

This virus seems to be highly host-specific and causes LSD in cattle (*Bos indicus* and *Bos taurus*) and water buffalo (*Bubalus bubalis*). *Bos taurus* is generally more prone to LSDV than *Bos indicus* and *Bubalus bubalis* (water buffalo).

Transmission

This virus is transmitted mainly through mosquitoes, ticks, flies specifically stable fly (Magori-Cohen et al. 2012; Paslaru et al. 2021). Entry of new animals to the naïve area or farm from affected one is also one of the major factors for spread of disease. This disease may also be spread through mechanical means like veterinary equipment, specifically needles etc.

Morbidity and Mortality

It is difficult to establish presence of virus in the field conditions due to which no reports are available on establishment of the incubation period in spontaneous cases. Morbidity rate varies from 5% to 45% and sometime it is up to 100% if outbreak occurs in naïve area. Mortality rate is not so high and varies from 10% to 15% but if outbreak occurs in naïve area, then mortality rate could rise up to 40%. Furthermore, both morbidity and mortality rates depend on the factors like age of the animal, its breed, immune status and in case of adult female cattle its production period (Wolff et al. 2022).

Geographical Distribution

LSD was reported for the first time in 1929 in Zambia (RAS 1930) and that was confined in the regions of Africa for 60 years. This disease remained endemic only in sub-Saharan

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Africa countries till 1990. Afterwards, it extended to North Africa and Middle East countries. This disease spread from southern Africa to Uganda from 1955 and 1960. After 2012, LSD spread sharply to Asia and Europe. In last fifteen years, a total of 3118 outbreaks of LSD reported in Africa, Europe and Asia. In Europe, 2265 outbreaks of LSD shared 72.6% of the total outbreaks, Asia shared 14.8% (462 outbreaks) of the total, while reported outbreaks were 391 in Africa region which shared 12.5% of the total outbreaks. It indicates that LSD have more outbreaks in Europe, Africa and Asia during last 10 years. Moreover, LSD outbreaks reported mostly occurred in summer season and highest in the month July as compare to other months of the year which corresponds to the high prevalence of vectors. Since 2012, around 3 (2.78) new countries per year are being affected by LSD (Alkhamis and VanderWaal 2016; Calistri et al. 2020). The morbidity is around 9-26% and mortality 1-10% in non-endemic regions (Ochwo et al. 2018; Sameea et al. 2017). However, morbidity reaches up to 85% in some LSD outbreaks and around 40 to 75% mortality was reported (Tuppurainen and Oura 2012; Wolff et al. 2022). Due to global spread of LSD in last decade, global coordination becomes inevitable to control and eradicate this transboundary disease.

Recently, LSD outbreak reported in Turkey and Russia and other countries in southern Europe. In Asia, first outbreak of LSD was reported to OIE in September 2019 in Bangladesh followed by China, Nepal, India, Vietnam, Hong Kong, and Myanmar (Badhy et al. 2021; Flannery et al. 2022; Gupta et al. 2020; Hasib et al. 2021). This disease is now considered one of the most economically important emerging livestock diseases in Bangladesh. In Thailand, LSD outbreak was confirmed and reported to WOAH officials on April 2021 (Arjkumpa et al. 2021, 2022).

Most recent outbreak occurred in Pakistan and first case was reported in Sindh province on November 08, 2021. This disease killed more than 570 cattle up to June 2022. This disease was then spread to Punjab Province of Pakistan and cases were reported in district Bahawalpur and Taunsa Sharif on February, 2022. Afterwards, this disease spread throughout the province. In Islamabad capital territory of Pakistan, LSD outbreak occurred on March 25, 2022. This disease is now spread throughout the country (unpublished data). No data is yet published which reports morbidity and mortality of animals due to LSD in Pakistan.

Clinical Signs

The incubation period of LSDV is 4 days to 5 weeks. Therefore, subclinical infections are common in the field. Clinical cases of the disease are tip of an iceberg if outbreak occurs. Severity of the disease is highly variable and depends on a lot of factors i.e., strain of capripoxvirus, breed and age of the host, immunological status of the animals. It is also observed that severity of the disease is more in naïve area and the lactating cattle. The clinical feature of the disease shows following signs and symptoms:

- Purulent or mucopurulent nasal discharge and lachrymation are the first signs to be observed.
- Excessive salivation containing high concentrations of virus.
- High rise in body temperature (>105 °F) which may persist to a week.
- Necrotic plaques are present in the mucous membranes of the oral and buccal cavities which lead to inappetence.
- Reduction in milk yield to a significant level.
- Loss of body weight.
- Enlargement of subscapular and pre femoral lymph nodes (Abutarbush and Tuppurainen 2018).
- Other prominent characteristics of the disease are development of circumscribed, firm nodules which are 10-70 mm in diameter specifically appear on the neck, shoulders, fore and hindlimbs, withers and tail as shown in Fig. 1B and C (Beard et al. 2010; Şevik and Doğan 2017).
- Predilection sites of nodules are skin of head, neck, perineum, genitalia, udder and limbs shortly after the beginning of fever (Fig. 1 B and C).
- Deep nodules involve all layers of the skin, subcutaneous tissue and sometimes even the underlying muscles (Şevik and Doğan 2017).
- Skin nodules may persist for several months after recovery (Fig. 2B and C).
- Necrotic and ulcerative nodules leads to the complication of myiasis (Namazi and Tafti 2021).
- Lameness is also prominent (Fig. 1A).
- Edema of the limbs especially forelimbs and lameness is also observed (Tuppurainen and Oura 2012).
- In worst cases, ulcerative lesions develop in cornea of eyes leading to blindness.
- Orchitis is also observed as complication.
- Involvement of the lungs may lead to pneumonia or it could be due to the secondary bacterial infections.
- Mastitis is a common complication (Al-Salihi and Hassan 2015).
- LSDV is also capable to induce abortion. However, aborted fetuses does not contain nodules (Constable et al. 2016).

Necropsy Findings

The post-mortem lesions of the LSDV affected animal are;

- Characteristic nodules on the skin of dead animals.
- There would be nodular lesions/impressions on the subcutaneous tissue.
- Lesions could also be present in the mucous membranes throughout the gastrointestinal tract (Zeynalova et al. 2016).
- In some cases, nodules may be present in lungs (Zeynalova et al. 2016).
- Hemorrhagic lesions are seen in spleen, liver or rumen.

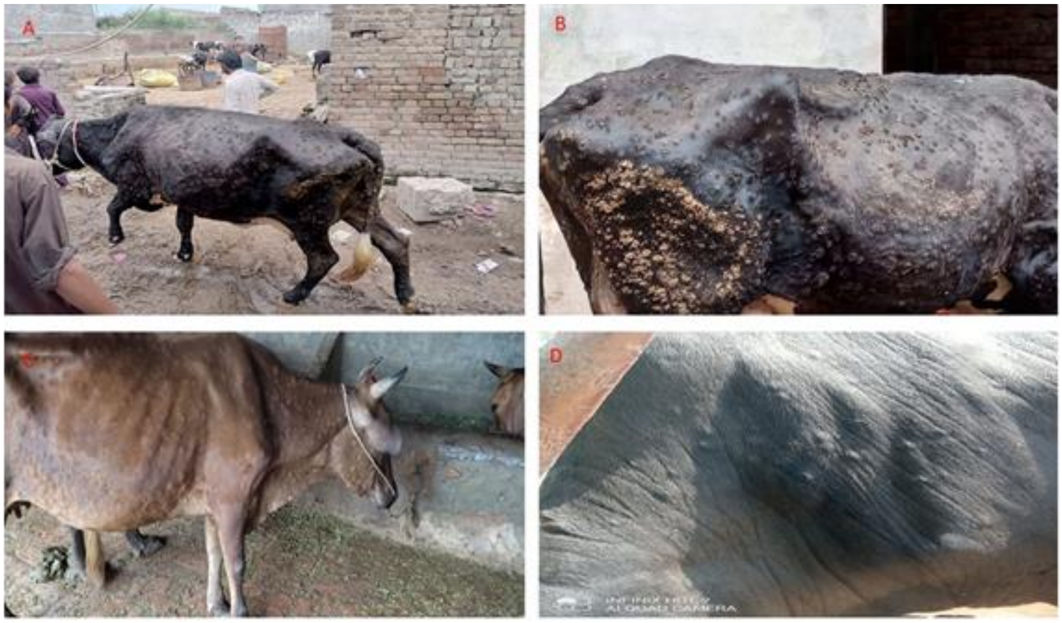

Fig. 1: Clinical signs of Lumpy Skin Disease from affected cattle and water buffalo in Pakistan.

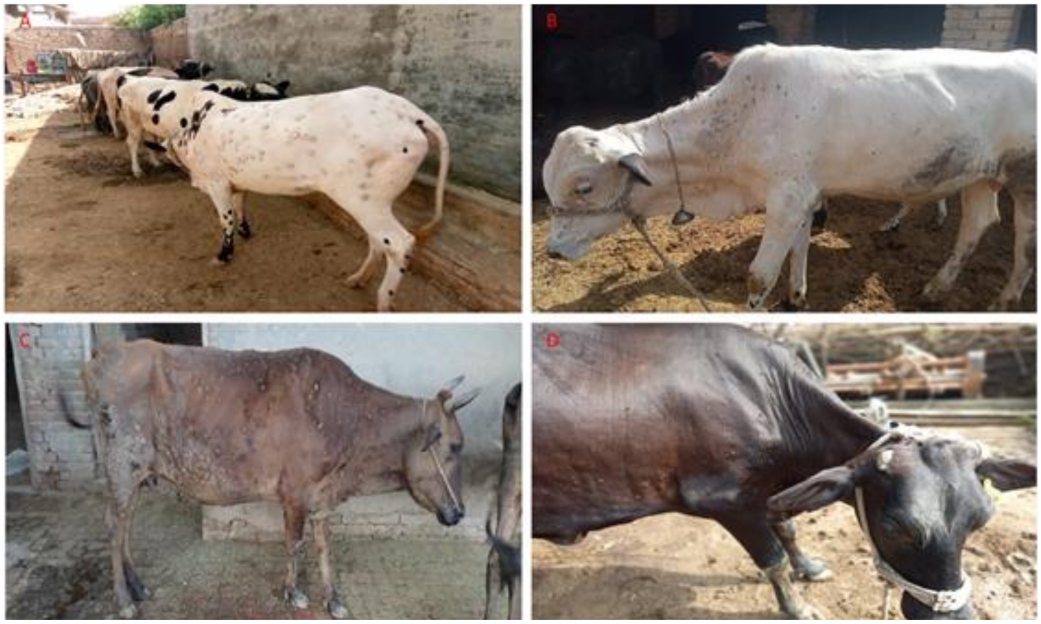

Fig. 2: Cattle recovered from Lumpy Skin Disease in Pakistan

LABORATORY Diagnosis

1. Sample Collection

A. General Rules

Following are the points of considerations for collection of samples for diagnosis of LSD (Tuppurainen et al. 2017; Anonymous 2021):

- Trained Personnel should collect sample.
- Protective clothing must be used for collection of samples.
- Animal should be restrained properly to avoid injury to the operator and animal itself.
- Care must be taken for aseptic preparation of the sample collection site. Sample should be taken with care to avoid contamination.
- Sufficient quantity of sample material should be collected.

- Sample must be collected by using appropriate techniques.
- Samples which have not yet been tested should be considered positive and handle accordingly.
- Proper labelling and packaging of the samples should be done.
- As LSD diagnosis is urgent, therefore, samples must be sent to the lab at appropriate temperature and transport through most direct route.

B. Sample Types

The preferred samples types for diagnosis of LSDV include skin lesions and scabs, saliva or nasal swabs and blood with and without EDTA (Tuppurainen et al. 2017).

2. Identification of the Virus

The gold standards for detection of antibodies raised against capripoxvirus is "Virus neutralization test". There is another highly sensitive and specific test for LSD diagnosis is "Western blot" but it is expensive and difficult to perform. Recently, a new kit is launched in the market for detection of antibodies of capripoxvirus with the name "capripoxvirus antibody enzyme-linked immunosorbent assay". This is also a suitable kit for quick diagnosis of LSDV. However, polymerase chain reaction (PCR) is widely used for detection of LSDV and also considered for authenticity (Tuppurainen et al. 2017).

Differential Diagnosis

Clinical characteristics of LSD are prominent enough for diagnosis; however, it is difficult to diagnose it at initial stage and may be confused with the following diseases (Constable et al. 2016; Tuppurainen et al. 2017; Anonymous 2021).

- Bovine herpes mammillitis (bovine herpesvirus 2; pseudo-lumpy skin disease)
- Bovine papular stomatitis (Parapoxvirus)
- Pseudo cowpox (Parapoxvirus)
- Cowpox virus (Orthopoxviruses)
- Dermatophilosis
- Demodicosis
- Insect or tick bites
- Rinderpest
- Hypoderma bovis infection
- Photosensitization
- Urticaria
- Cutaneous tuberculosis

Treatment

There is no specific treatment of LSD. However, symptomatic treatment is practiced along with preventive measures (Constable et al. 2016). Following treatment regimen is recommended;

- Administer antipyretics e.g., flunixin meglumine, meloxicam, ketoprofen etc. for lowering the temperature and to keep up the appetite of diseased animals (Al-Salihi 2014; Das et al. 2021).
- Administration of broad-spectrum antibiotics are recommended i.e., amoxicilin, amoxicillin+clavulanic acid, ceftiofur sodium, florfenicol etc. to prevent secondary infection like pneumonia, mastitis, dermatitis, etc. (Al-Salihi 2014; Das et al. 2021).
- Antihistamines (e.g., Chlorpheniramine) can be to prevent pruritus and irritation.
- Intravenous fluids i.e., dextrose 5% along with vitamins and amino-acids should be administered to starved animals to support energy level. Intractable anorexia is a major contributing factor in delayed recovery and death.
- The exposed animals should be administered with immnomodulators (e.g., Levamisole @ 2.5-3.5 mg/kg on alternate days for 2 weeks) to help the animals to overcome the disease.
- For wound management, EUSOL (Edinburg University Solution of Lime) is easy to spray on wounds. This solution is prepared by making a paste of 12.5 g chlorinated lime and 12.5 g boric acid powder in 100 mL of water to form a paste and then add 1 liter of water to make the solution. EUSOL is commonly used for dressing the wounds in human and animals. It is safe as well as economical (Rai et al. 2023).
- Zinc sulphate @ 1-3 g/day for 2 weeks is also recommended to improve hide quality.

Zoonoses

LSD does not possess zoonotic importance. Infected animals are not source of infection for human through any means like milk and meat. However, milk should be consumed after boiling/pasteurization and meat should be well-cooked before consumption (Onono et al. 2019).

Prevention and Control

The stamping-out of the affected animals, biosecurity of the farms, restrictions on the mobility of animals from hotspot areas to the naïve area and vaccination are recommended as components of preventive and control strategies (Tuppurainen et al. 2017). To this end, following measures can be adopted for prevention and control of LSD;

- Movement of live animals from affected or hotspot zone to the naïve area or country is the major reason of spread of LSD. A careful clinical examination by the experts can help in minimizing the risk of introduction of the disease to the naïve area. Additionally, quarantine facilities should be strengthened especially in the country which are importing cattle from others. Cattle must be held in quarantine area for

5 to 7 days, so that, animals can be monitored in detail. Quarantine labs should also be equipped with the advanced technology where serological tests and PCR can be performed to rule out the diseases (Namazi and Tafti 2021).

- Non-vaccinated animals should be prohibited to move across the country whereas vaccinated animals should be allowed to move 3-4 weeks' post-vaccination.
- Education of veterinarians, livestock farmers and workers would be helpful in timely diagnoses of LSD which would be helpful to slow down the spread of disease.
- Compulsory and consistent vaccination is the only effective way to control LSD (Şevik and Doğan 2017).
- The control of vector is important for limiting the spread of LSD. Animal premises as well as animals should be targeted for vector control. Animal and premises should be sprayed with insect repellant which are safe for animals as well as for environment.

Immunization

- Cross-hybridization of DNA between three species of Poxviridae provides serologic cross-protection to each other. Live attenuated heterologous vaccine (goat/sheep pox vaccine) is, therefore, recommended and reportedly effective against LSD. Hence, it is used to protect cattle against LSDV. However, complete immunity against LSD is not provided by sheep pox vaccines (Namazi and Tafti 2021).
- The use of live vaccines is efficient to control the disease because these vaccines produce a strong and long-lasting immune response. However, development of local inflammation and skin lesions are reported with the use of live vaccines (Tuppurainen et al. 2017; Wolff et al. 2022).
- Advanced generation of capripoxvirus vaccines has been developed in which LSDV is used as a vector and provides dual protection through expression and delivery of immuno-protective proteins (Boshra et al. 2013; Wallace and Viljoen 2005). These vaccines also provide opportunity to target the immunomodulatory genes hence improve immune response of the animal (Kara et al. 2018).

Conclusion

Lumpy skin disease (LSD) is a highly contagious viral disease of cattle and buffalo that causes relatively low mortality. It does not affect humans. The disease can result in animal welfare issues and significant production losses. The diagnosis can be made through serological i.e., ELISA and molecular techniques i.e., PCR. The stamping-out of the affected animals, biosecurity of the farms, and vaccination are recommended as components of preventive and control strategies. The recent spread of the disease into disease-free areas indicates its epidemiological and economic significance and need appropriate preventive measures to control its spread.

REFERENCES

Abutarbush SM and Tuppurainen ESM, 2018. Serological and clinical evaluation of the Yugoslavian RM65 sheep pox strain vaccine use in cattle against lumpy skin disease. Transboundary and Emerging Diseases 65(6): 1657-1663.

Al-Salihi KA, 2014. Lumpy Skin Disease: Review of literature. Mirror of Research in Veterinary Sciences and Animals 3(3): 6-23.

Al-Salihi KA and Hassan IQ, 2015. Lumpy Skin Disease in Iraq: Study of the Disease Emergence. Transboundary and Emerging Diseases 62(5): 457-462.

Alkhamis MA and VanderWaal K, 2016. Spatial and temporal epidemiology of lumpy skin disease in the Middle East, 2012-2015. Frontiers in Veterinary Science 3: 19.

Anonymous, 2021. OIE-Listed diseases, infections and infestations in force in 2021. *https://www.oie.int/en/animal-health-in-the-world/oie-listed-diseases-2021*.

Arjkumpa O et al., 2021. First emergence of lumpy skin disease in cattle in Thailand, 2021. Transboundary and Emerging Diseases 68(6): 3002-3006.

Arjkumpa O et al., 2022. The First Lumpy Skin Disease Outbreak in Thailand (2021): Epidemiological Features and Spatio-Temporal Analysis. Frontiers in Veterinary Science 8: 799065.

Badhy SC et al., 2021. Molecular characterization of lumpy skin disease virus (LSDV) emerged in Bangladesh reveals unique genetic features compared to contemporary field strains. BMC Veterinary Research 17: 61.

Beard PM et al., 2010. A description of two outbreaks of capripoxvirus disease in Mongolia. Veterinary Microbiology 142(3-4): 427-431.

Boshra H et al., 2013. Capripoxvirus-vectored vaccines against livestock diseases in Africa. Antiviral Research 98(2): 217-227.

Calistri P et al., 2020. Lumpy skin disease epidemiological report IV: data collection and analysis. European Food Saftey Authority Journal 18(2): 6010.

Constable PD et al., 2016. Veterinary Medicine : A textbook of the diseases of cattle, horses, sheep, pigs and goats, 11th Ed., Elsevier, St. Louis, Missouri, USA.

Flannery J et al., 2022. A novel strain of lumpy skin disease virus causes clinical disease in cattle in Hong Kong. Transboundary and Emerging Diseases 69(4): e336-e343.

Givens MD, 2018. Review: Risks of disease transmission through semen in cattle. Animal 12(1): 1-7.

Gupta T et al., 2020. A review: Lumpy skin disease and its emergence in India. Veterinary Research Communications 44(3): 322-333.

Hasib FMY et al., 2021. Lumpy skin disease outbreak in cattle population of Chattogram, Bangladesh. Veterinary Medicine and Science 7(5): 1616-1624.

Kara PD et al., 2018. Characterisation of putative immunomodulatory gene knockouts of lumpy skin disease virus in cattle towards an improved vaccine. Vaccine 36(31): 4708-4715.

Magori-Cohen R et al., 2012. Mathematical modelling and evaluation of the different routes of transmission of lumpy skin disease virus. Veterinary Research 43(1): 1.

Das M et al., 2021. An updated review on lumpy skin disease: perspective of Southeast Asian countries. Journal of Advanced Biotechnology and Experimental Therapeutics 4: 322-333.

Namazi F and Tafti KA, 2021. Lumpy skin disease, an emerging transboundary viral disease: A review. Veterinary Medicine and Science 7(3): 888-896.

Ochwo S et al., 2018. Spatial and temporal distribution of lumpy skin disease outbreaks in Uganda (2002-2016). BMC Veterinary Research 14(1): 174.

Onono J et al., 2019. Knowledge of pastoralists on livestock diseases and exposure assessment to brucellosis within rural and peri-urban areas in Kajiado, Kenya. Research 8: 1916.

Paslaru AI et al., 2021. Potential mechanical transmission of Lumpy skin disease virus (LSDV) by the stable fly (Stomoxys calcitrans) through regurgitation and defecation. Current Research in Insect Science 7(1): 1407.

Rai L et al., 2023. A Comparative study between use of topical honey and Edinburgh University's solution of lime (EUSOL) dressing in necrotizing fasciitis wounds. Cureus 15(1): e33825.

RAS M, 1930. Pseudo-urticaria of cattle. Northern Rhodesian Department of Animal Health, Annual Report 1930: 20-21.

Sameea YP et al., 2017. Epidemiological Study of Lumpy Skin Disease Outbreaks in North-western Iran. Transboundary and Emerging Diseases 64(6): 1782-1799.

Şevik M and Doğan M, 2017. Epidemiological and Molecular Studies on Lumpy Skin Disease Outbreaks in Turkey during 2014-2015. Transboundary and Emerging Diseases 64(4): 1268-1279.

Shen YJ et al., 2011. A novel candidate HIV vaccine vector based on the replication deficient Capripoxvirus, Lumpy skin disease virus (LSDV). Virology Journal 8: 265.

Sprygin A et al., 2019. Transmission of lumpy skin disease virus: A short review. Virus Research 269: 197637.

Tuppurainen ESM and Oura CAL, 2012. Review: Lumpy Skin Disease: An Emerging Threat to Europe, the Middle East and Asia. Transboundary and Emerging Diseases 59(1): 40-48.

Tuppurainen ESM et al., 2017. Review: Capripoxvirus Diseases: Current Status and Opportunities for Control. Transboundary and Emerging Diseases 64(3): 729-745.

Tuppurainen ESM et al., 2017. Lumpy Skin Disease; A field Manual for Veterinarians. Food and Agriculture Organization of the United Nations, Rome.

Wallace DB and Viljoen GJ, 2005. Immune responses to recombinants of the South African vaccine strain of lumpy skin disease virus generated by using thymidine kinase gene insertion. Vaccine 23(23): 3061-3067.

Wolff J et al., 2022. Characterization of a nigerian lumpy skin disease virus isolate after experimental infection of cattle. Pathogens 11(1): 16.

Zeynalova S et al., 2016. Epizootology and molecular diagnosis of lumpy skin disease among livestock in Azerbaijan. Frontiers in Microbiology 7: 1022

Bovine Ephemeral Fever (BEF)

AUTHORS DETAIL

Rehan Ashraf[1*], Saba Rashid[1], Manahil Riaz[1], Misha Salam Bajwa[1], Aamina Jamil[1] and Muhammad Touseef Khalid[1]

[1]Faculty of Veterinary Medicine, University of Agriculture, Faisalabad
*Corresponding author: drrehanashrafbandesha@gmail.com

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INTRODUCTION

Bovine ephemeral fever, which is also known as three days sickness, is a viral disease transmitted by arthropods. It is also known by the various other names such as bovine epizootic fever, dengue of cattle and three days stiff sickness (George and Standfast 2019). The causative agent is bovine ephemeral fever virus (BEFV) which is single-stranded RNA virus and belongs to the genus *Ephemerovirus* and family *Rhabdoviridae* (Lee 2019). Occurrence of the disease has expanded over a wide range of area ranging from Africa to the Nile River, South Asia to Middle East, Korea, Taiwan, and Southern Japan (Walker and Klement 2015).

The disease was found to be most prevalent in humid and plain areas. BEF could be one of the most significant bovine diseases in the dairy and meat industries of Thailand. In 1974, BEF outbreaks in Iran led to the discovery of bovine ephemeral fever virus (BEFV), which was first isolated from the blood of cattle at the time. In 1985, Turkey saw its first BEF outbreak. The BEF has returned in Southern and Southeastern Turkey in 1996, 1999, 2005, 2008 and 2012 (Feray Alkan 2017).

The genome of the BEF virus is composed of enveloped G protein and four non-membranous proteins. These proteins are N protein, L protein, P protein, and M protein. The G protein is structurally like the G proteins of all other animal rhabdoviruses. Virion polymerase transcription of messenger RNA (mRNA) from genomic RNA is the initial step in replication. Entering a cell and recognizing the receptors are exclusively done by Glycoprotein of virus (G protein). Individual rhabdovirus cell receptors have yet to be discovered in detail.

Viremia titer is highest in blood 24 hours before an increase in interferon levels in serum and neutrophil numbers. Virus is detectable after 43 hours preceding to inoculation. Virus replicates exclusively in the vascular endothelium during the prepatent duration of 29 hours or fewer. Calves that are less than 3 to 6 months are the least affected and do not show any clinical signs of illness. Mortality is relatively uncommon, and it is usually less than 1% of the herd (Uren et al. 1992).

Generally, disease affect the health of animal and causes a sudden increase in body temperature. The three-day fever virus enters the body and creates polynuclear neutrophils in the blood after 24 hours. Lesions and clinical signs are due to the infection in endothelial cells and hypocalcemia is linked with it. The disease does not spread through intrauterine administration of the virus or semen. Joint involvement varies greatly; however, it might include the articular surfaces of the limbs and the spinal column (Dinter and Morein 1990). Some renal tubule epithelial linings show minor degenerative alterations such as vacuolation and pyknosis (Bai 1991). Hyperplasia of the intima with thrombus development affects several of the blood arteries. Muscle fibers are deteriorated and necrosed in some places. Domestic cattle and buffaloes are the primary hosts of three-day fever (BEF) (Wang et al. 2001). Infected wild ruminants (wildebeest, eland and buffalo) generally show no symptoms (Lee F 2019).

BEF has a significant economic impact, ranging from mortality to trade consequences between and within countries (Yang et al. 2018). The Bovine Ephemeral Fever (BEF) virus poses a serious threat to both domestic and international animal traffic. Animals which are not previously exposed to BEF and has no antibodies against it, are required in BEF endemic areas to neutralize the impact of disease (Zahid et al. 2019). The cost of a BEF outbreak in Israel in 1999 was estimated to be $112 per non-lactating cow and $280 per lactating cow. Virus can be identified within three to four days of infection (Chaisirirat et al. 2018).

Vaccination is the only method to control and prevent the disease. Most vaccines' protective immunity seems to have a short half-life, which could make them ineffective unless further booster doses are given at intervals of six months to a year (Lapira 2018). The virus that causes bovine ephemeral fever has no specific treatment, however, symptomatic treatment is possible (Taghipour Bazargani et al. 2013). Nonsteroidal anti-inflammatory medicines are used as palliative care to relieve symptoms (St George 1997). Cows exhibiting hypocalcemia should receive parenteral treatment with calcium borogluconate.

History

Three-day sickness has been observed in a lot of tropical and subtropical locations worldwide (Walker 2005). In Australia, Asia, Africa, and the Middle East, bovine ephemeral fever is

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enzootic and occasionally epizootic. BEFV is absent from the America, the Pacific Islands, New Zealand, and Europe. Though, all regions of these nations have not been affected, it is likely to have affected cattle across all the Africa, the Arabian Peninsula, and South Asia including Lebanon, Iran, Pakistan, India, Burma, Bangladesh, Iraq, Japan and Eastern and Southern China (Sayed-Ahmed 2005). The geographical distribution of bovine ephemeral fever virus (BEFV) has been shown in Fig. 1 and morbidity and case fatality due to BEFV has been enlisted in Table 1.

Etiology

Bovine Ephemeral fever is caused by the Bovine ephemeral fever virus (BEFV). BEFV is an arthropod, vector, borne rhabdovirus, a member of the genus *Ephemerovirus*, and belongs to the family *Rhabdoviridae* (Daniels et al. 1995).

Classification

The *Rhabdoviridae* family is classified into the four genera consisting of animal viruses i.e., *Ephemerovirus*, *Lyssavirus*, *Novirhabdovirus*, and *Vesiculovirus*. Two genera including *Nucleorhabdovirus* and *Cytorhabdovirus* contain plant infecting viruses But the Bovine ephemeral fever virus and other viruses (serologically different) that infect cattle but are not harmful are included in the *Ephemerovirus* genus (Daniels et al. 1995). Fig. 2 distinguishes individual species of the family *Rhabdoviridae* serologically and genetically.

Virion Properties

Virion is approximately 70 nm (60 to 80 nm) in diameter and 145 nm (120 to 170 nm) in length. BEFV is surrounded and enveloped by glycoprotein spikes and contains a helically coiled cylindrical nucleocapsid. The characteristic cylindrically shaped nucleocapsid gives virion its characteristic conical or bullet shape appearance. One end is more tapered compared to the round forms of rabies virus (RABV) or vesicular stomatitis virus (VSV).

Molecular Structure

Nucleocapsids contain a single 11-15 kilobyte molecule of a linear, negative-sense, single-stranded RNA genome. The virus contains the five major rhabdovirus structural proteins. Single envelope protein is G protein and four non-membranous proteins are N protein, L protein, P protein and M protein.

G protein is the glycoprotein trimers make surface spikes on the envelope that aid in resistance as it is immunogenic in nature.

N protein is a nucleoprotein gene and encodes for the major component of the virion nucleocapsid

P phosphoprotein act as a polymerase cofactor for virus

L (large multi-functional) enzyme act as RNA polymerase in the transcription and replication of RNA.

M (matrix) protein is the inner protein of virion binds to the glycoprotein of the cytoplasmic domain and to the nucleocapsid to facilitate the budding of the virion.

Along with these rhabdovirus structural proteins, the genome of BEFV features a region containing multiple additional ORFs (open reading frames) between L and G genes.

Thus, the BEFV genome comprises a total of 10 ORFs arranged in the negative sense in order of 3′-N-P-M-G-[Gns-α1-α2-β-γ]-L-5′ (Walker and Klement 2015) as shown in Fig. 3.

Fate of the BEF Virus

The biological cycle of the virus starts when the insect vector secretes the virus in saliva. When *Culicoides* lacerate the dermis and capillaries with their mouthpart virus present in the saliva is mixed in the blood pool. The lymphatic system at the site drains the virus into the body (Mullen and Durden 2009). But this route is not effective for infection as the viruses do not appear in lymph with an exception of one case reported.

Mosquitoes are thought to be a more efficient vector for transmission as mosquitoes locate the small blood vessels in the dermis before piercing the dermis. In this way, the virus is directly injected into the bloodstream (intravenous route). After the onset of infection, the initial phase of multiplication is not well defined. Using cell cultures of *Aedes albopictus* as an assay system, virus is detectable after 43 hours, preceding inoculation. By sub-inoculation the virus is detectable after 29 hours. Viremia titer is highest in blood 24 hours before an increase in interferon levels in serum and neutrophil numbers and 36 hours before the onset of early clinical signs and pyrexia (Uren et al. 1992).

A consistent viral replication take place exclusively in the vascular endothelium (4 or 5 cycles) during a prepatent duration of 29 hours or fewer. BEF virus found on or inside the neutrophils in the bloodstream or in the serous cavities. As a result of regular phagocytic activity of these cells', virus is conveyed passively in the body (St George 1992).

Clinical Signs

The disease has a short incubation period, around 36 to 48 hours under normal conditions. This may vary from 29 hours to 10 days under the experimental conditions but the average is usually about 3 to 4 days (Akakpo 2015). Calves that are less than 3 to 6 months of age are the least affected and do not show any clinical signs of illness. Bulls, overweight cows, and highly producing cows are mostly affected. Mortality is relatively uncommon and it is usually less than 1% of the herd. The disease is acute in most cases (Constable et al. 2016). The disease affects health in general and causes a sudden increase in body temperature. Generally, fever occurs in two phases. The clinical signs are not significant and hard to detect during the first phase of hyperthermia. In animals, that are affected more severely there is a sudden onset of fever (40-41°C) along with loss of appetite,

Table 1: Morbidity and case fatality of bovine ephemeral fever *outbreaks or epidemic*

Year	Country	Morbidity (%)	Case Fatality (%)	References
1967	Taiwan	26.6	5.2	(Hsieh 2005)
1983–1984	Taiwan	20.1	6.0	(Hsieh 2005)
1989–1990	Taiwan	14.5	5.0	(Hsieh 2005)
1990	Israel	8.3–20.0	2.0	(Yeruham et al. 2010)
1996	Saudi Arabia	59	>1.0	(Abu Elzein et al. 1999)
1996	Taiwan	13.6	11.3	(Hsieh 2005)
1999	Taiwan	5.6	21.9	(Hsieh 2005)
1999	Israel	5.4–38.7	8.6–28.0	(Yeruham et al. 2010)
2001	Taiwan	7.4	9.7	(Hsieh 2005)
2001	Taiwan	15.0	50.0	(Hsieh 2005)
2004	Israel	14.9–22.2	3.5–5.4	(Yeruham et al. 2010)
Before 2000	China	10.0–20.0	>1.0	(Zheng and Qiu 2012)
2011	China	30.0	5.0	(Zheng and Qiu 2012)
2012	Turkey	35.0	15.0–20.0	(Tonbak et al. 2013)
2013	Iran	17.0	25.8	(Mirzaie et al. 2017)
2015	Japan	28.9	0.0	(Hirashima et al. 2017)

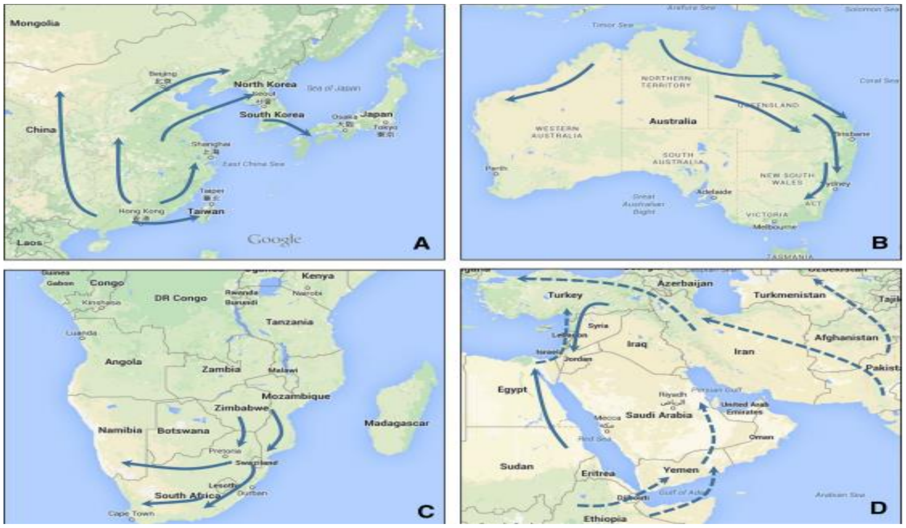

Fig. 1: Likely general directions of the seasonal spread of BEFV. A) East Asia. B) Australia. C) Southern Africa. D) Middle East. Epizootics appear to emerge in the spring or early summer from enzootic foci in tropical regions and extend northwards or southwards through late summer and autumn. Pathways shown in East Asia and Australia are based on historical records and recent observations of epizootics, supported by molecular epidemiological studies. Pathways in Africa are based only on historical accounts. Pathways in the Middle East are less clear and may be complex with the potential for epizootics to originate in either East Africa or West Asia. Dashed arrows indicate possible pathways in this region" (Walker and Klement 2015).

depression, anorexia, nasal discharge, salivation, stiff gate, swollen joints, rapid respiration and pulse rate, edema of the head, eye socket, and subcutaneous muscles and shivering. Sometimes, the animal lay on its side and sometimes in sternal recumbency. Animal shows some reflexes but these reflexes disappear gradually with the progression of the disease. Lack of rumination, loss of the swallowing reflex, profuse salivation, and constipation become evident. In lateral recumbent animals there is a total gradual loss of reflexes leading to coma and death of the animal. However, it should be emphasized that these clinical symptoms could go as quickly as they appeared. After 12-24 hours of the 1st peak of fever, there is the 2nd peak of fever which causes lacrimation and affects the lungs causing rattling and tachypnea. Secondary complications may occur which include pulmonary emphysema and pneumonia, stiffness of the limbs, abundant discharge, lameness, arthritis, and lasting paresis which forces the animals into prolonged sternal recumbency. This phase of fever may persist for 2-4 days. Other clinical signs may appear or persist along with the fever which may include subclinical mastitis which leads to a marked reduction in milk yield, infertility in the bulls, and abortion in the 5 percent of pregnant cows. Following a gradual loss of reflexes, the disease can lead to death in recumbent animals. Other animals recover without complications (persistent stiffness of the limbs, locomotor ataxia, pulmonary emphysema) in 5-6 days. In recovered milking cows, milk yield is always less than it was before the onset of the disease (Akakpo 2015). The course of disease has been shown in Fig 4.

Transmission

A lot of work has been done in recent years but the vector list is not clearly defined. Disease vectors may include biting midge *Culicoides brevitarsis* and mosquitoes of *Aedes* spp., *Anopheles (A.) bancroftii*, *A. annulipes* and *Culex (C.) annulirostris*. In Australia, *C. annulirostris* has been identified as a biological vector. Epidemiology of the disease in Australia supports the spread of the disease by mosquitos rather than the biting midges. *C. annulirostris* can transmit the infection within a week by feeding on an infected animal.

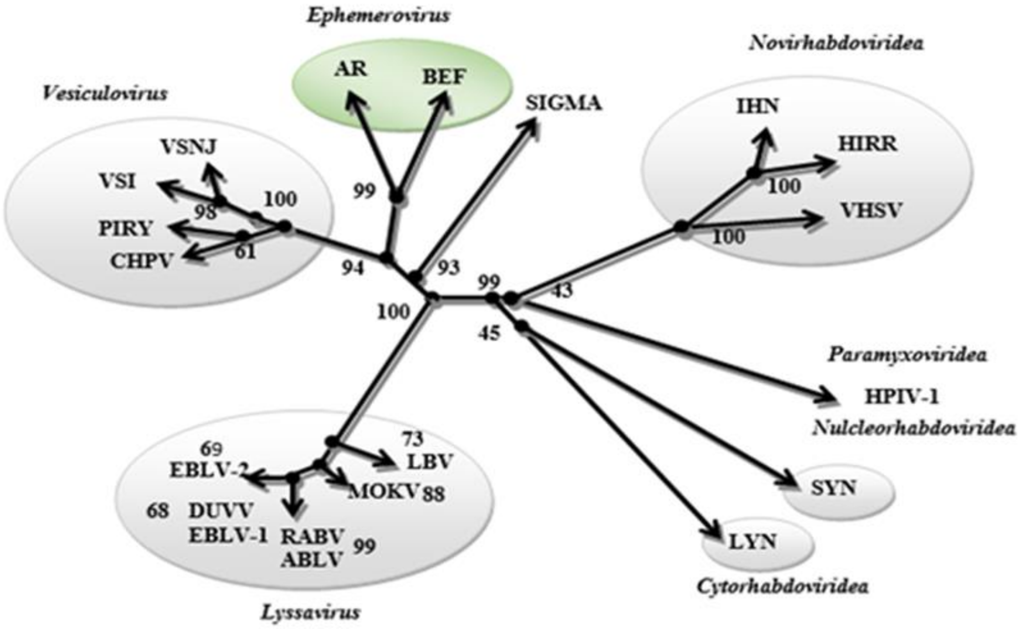

Fig. 2: Phylogenetic relationships of *Rhabdoviridae* Family on the basis of conserved portion of N protein abbreviations: "ABLV, Australian bat lyssavirus; ARV, Adelaide River virus; BEFV, bovine ephemeral fever virus; CHPV, Chandipura virus; DUVV, Duvenhage virus; EBLV, European bat lyssavirus; HIRRV, Hirame rhabdovirus; HPIV, human parainfluenza virus; IHNV, infectious hematopoietic necrosis virus; LBV, Lagos bat virus; LYNV, lettuce necrotic yellows virus; MOKV, Mokola virus; PIRYV, Piry virus; RABV, rabies virus; SIGMAV, Sigma virus; SYNV, Sonchus yellow net virus; VHSV, viral hemorrhagic septicemia virus; VSIV, vesicular stomatitis Indiana virus; VSNJV, vesicular stomatitis New Jersey virus." [From Virus Taxonomy: Eighth Report of the International Committee on Taxonomy of Viruses (C. M. Fauquet, M. A. Mayo, J. Maniloff, U. Desselberger, L. A. Ball, eds.), p. 642. Copyright © Elsevier (2005), with permission.]" (Maclachlan et al. 2016).

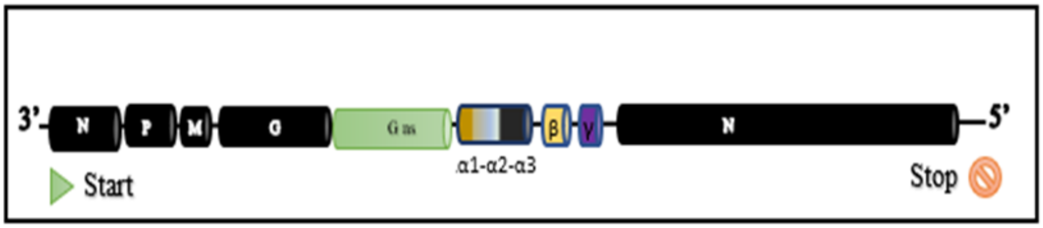

Fig. 3: Structural organization of BEFV genome, arranged in a negative sense. The Black color displays structural proteins and all accessory genes are displayed in different colors

In affected nations where the vectors are active all year long, three-day fever appears as a sporadic or enzootic disease. In favorable seasons, the prevalence rises as the number of arthropod vectors grow. Cattle are the reservoir host. Other than cattle, the reservoir host has not been identified yet. The spread of the disease-causing virus by the wind-born carriage of vectors has been identified (Aziz-Boaron et al. 2012). Through animal transport, transboundary movement can also occur but the transmission does not occur through direct contact with the infected animal or their ocular discharge or saliva. The disease does not spread through intrauterine administration of the virus or semen. Experimentally the disease can be transmitted by whole blood transfusion or leukocyte administration through an intravenous route. Viremia lasts for three days to a maximum of two weeks and there is no carrier state observed experimentally (Constable et al. 2016).

Pathogenesis

The three-day fever virus enters the body and creates polynuclear neutrophils in the blood 24 hours later. Lesions and clinical signs are due to the infection in endothelial cells and hypocalcemia is linked with it. High-level interferon production by the infected cells leads to toxemia and inflammation in blood vessels, mucosa, and joints. Plasma fibrinogen is observed in the peritoneum, joints, cardiac and pleural cavities. A sharp decrease in calcium levels of blood leads to nerve paralysis (Akakpo 2015).

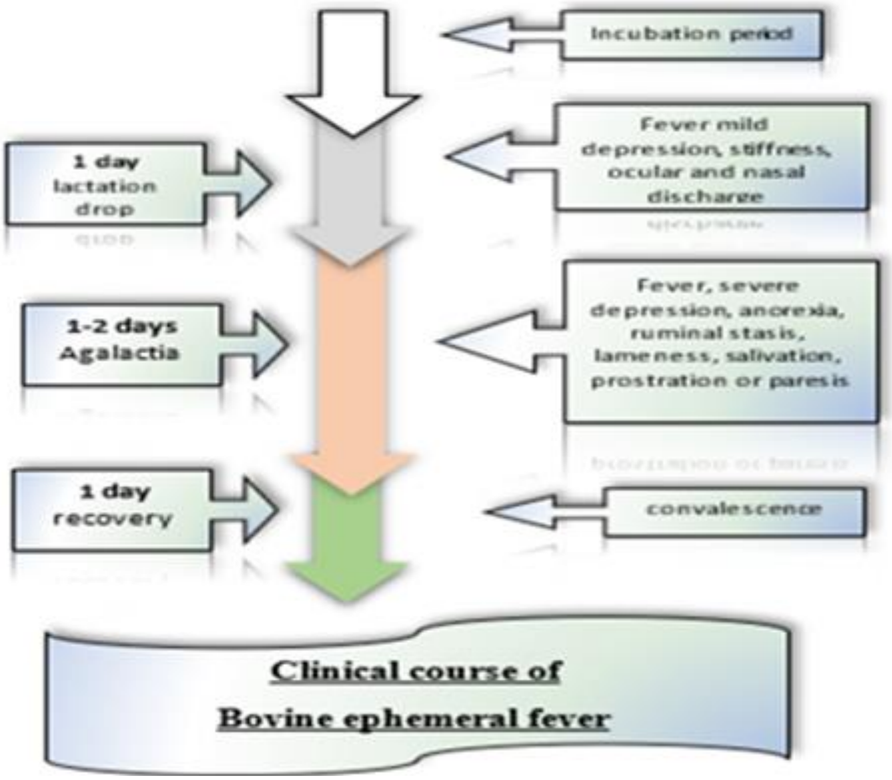
Incubation period
Fever mild depression, stiffness, ocular and nasal discharge
1 day lactation drop
1-2 days Agalactia
Fever, severe depression, anorexia, ruminal stasis, lameness, salivation, prostration or paresis
1 day recovery
convalescence
Clinical course of Bovine ephemeral fever

Fig 4: Course of Bovine Ephemeral Fever

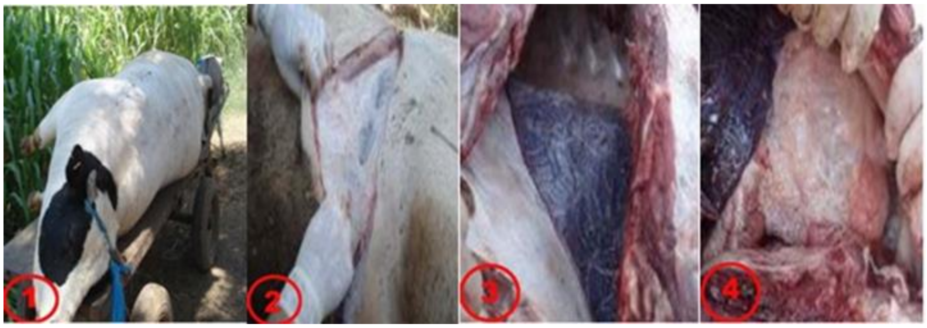

Fig. 5: A dead calf showing severe subcutaneous emphysema involving the whole body: Fig. 5.2: Subcutaneous fascia of a dead calf showing emphysema: Fig. 5.3: Lung showing interstitial and pulmonary emphysema: Fig. 5.4: Thickened, opaque and emphysematous pericardium.

Gross Pathology

According to studies, severe subcutaneous emphysema, encompassing the entire body is usually present. Emphysematous, thicker and pale subcutaneous fascia can be observed. BEFV causes a diffuse hemorrhage in the pharyngeal area. Marked pathological changes in the lungs are observed due to BEFV infection. Lung lobes may be mosaic in appearance, cyanosed and edematous. Interstitial pulmonary edema is a prominent pathological finding in some lobes of the lungs. In interlobular septa and subpleural septa, emphysema appears as small vesicles. Engorgement of the spleen and kidneys is possible. Urine and bladder appear to be normal. The neurological symptoms are not due to any prominent or microscopic brain abnormalities. Joint involvement varies greatly; however, it might include the articular surfaces of the limbs and the spinal column (Dinter and Morein 1990). Mediastinal and bronchial lymph nodes are congested and enlarged. Serous membranes such as pericardium, peritoneum, and pleura are emphysematous, opaque, and thickened. Focal congestion is usually observed in the endocardium. The gall bladder can be enlarged to a greater extent. There are no marked changes on muscles. Mild congestion in the kidneys may be present (El-Nesr et al. 2010). Fig. 5 highlighted the presence of various pathological changes in the body of a dead calf (El-Nesr et al. 2010).

Histopathology

Lung

There is mild degeneration of the epithelium of bronchioles and bronchi with early necrotic changes. Epithelium of bronchi is fully destroyed and inflammatory changes are minimal. The presence of cellular debris inside some bronchioles results in the obliteration of a few bronchial lumens.

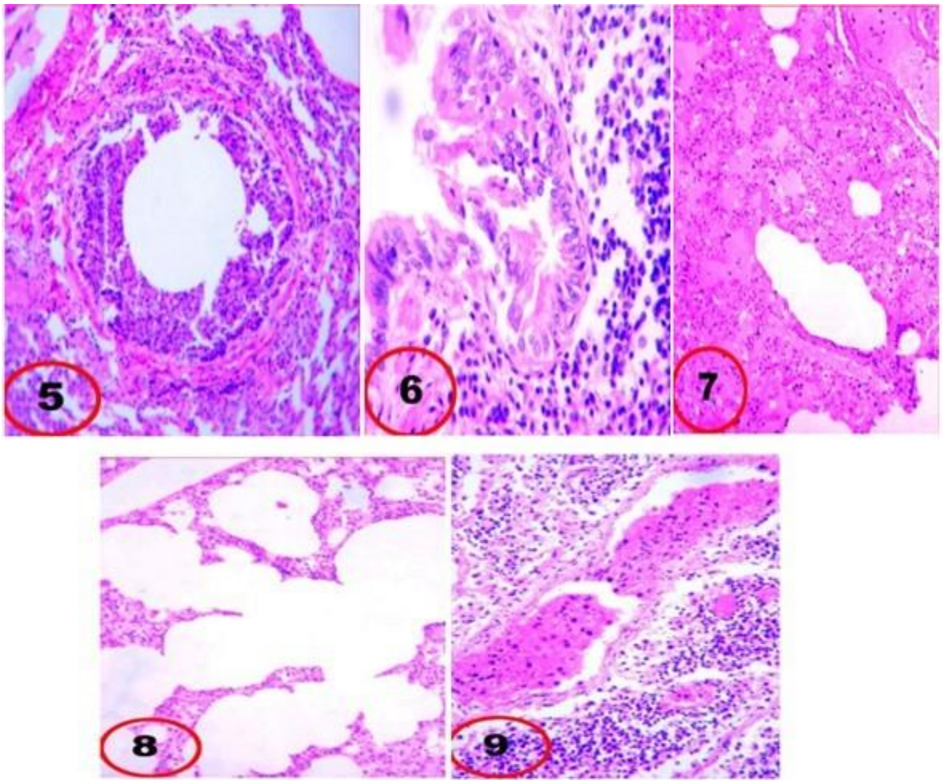

Fig. 6: Lung tissue showing cellular debris within bronchiolar lumen (H&E-X 100): Fig. 6.2: Lung tissue showing focal leucocytic aggregations adjacent to the bronchi and bronchioles (H&E-X 400): Fig. 6.3: Lung tissue showing completely filled alveoli with proteinaceous fluid" (H&E- X40): Fig. 6.4: Lung tissue showing interstitial and alveolar emphysema (H&E- X40): Fig. 6.5: Lymph node showing congested blood vessel (H&E-X100)

The alveolar epithelium is detached in some locations, resulting in an accumulation of desquamated cells within the alveolar lumen. Tunica media degradation is also evident due to focal leucocytic aggregations made up of macrophages and a few neutrophils, which are seen in some places, particularly those adjacent to bronchi and bronchioles. Occasionally, there is necrosis of the peribronchial lymphoid aggregations. There are signs of apoptosis in some bronchial and alveolar epithelial cells. Many alveoli appear to have a hyalinized membrane lining them. All cases with angiopathy show dilated and congested blood arteries, some of which have necrotic alterations in the intima and endothelial cells floating within the lumen. In the interstitial tissue, there is subintimal edema and, in some regions, substantial edematous alterations, with few inflammatory cells. Proteinaceous fluids fill the alveoli in large areas. The alveoli are significantly overfilled with air, and some of them rupture, resulting in interstitial and alveolar emphysema. Atelectasis develops in the neighboring alveoli (El-Nesr et al. 2010). Fig. 6 shows pathological changes taking place in lungs.

Lymph Nodes

The germinal center of certain lymphoid follicles has moderate hyperplasia and necrobiosis. Blood vascular congestion is very common. Hemorrhage and hemosiderosis have been seen in parts of the cortex and medulla. Hyperplasia of the intima with thrombus development affects several of the blood arteries. In the medulla, vasculitis is observed. In some parts of the stroma, there is a small amount of protein-rich edematous fluid. The paracortex and the medullary cords both have a small number of neutrophils (El-Nesr et al. 2010).

Kidneys

Some renal tubular epithelial linings show minor degenerative alterations such as vacuolation and pyknosis in a few nuclei. The blood arteries are usually dilated and clogged (El-Nesr et al. 2010).

Intestine

There is hyperplasia of lymphoid follicles and catarrhal enteritis is usually observed (El-Nesr et al. 2010).

Tongue

Dermal blood arteries are clogged, with some of them thrombosed (El-Nesr et al. 2010).

Skeletal Muscles

Muscle fibers are deteriorated and necrosed in some places. The interstitial region between the muscle bundles have become edematous (El-Nesr et al. 2010).

Liver

Vacuolar degeneration has been seen throughout the parenchyma of liver cells. The portal blood arteries and central veins are dilated and clogged (El-Nesr et al. 2010).

Heart

Blood arteries in the subendocardial area and myocardium are clogged. The cardiac muscles show only minor deterioration (El-Nesr et al. 2010).

Epidemiology

'Epizootic dengue fever of cattle' was the title of the first clinical report of 'three days sickness' of cattle or ephemeral fever (St George 1992). Numerous ruminant species have been shown to have neutralizing antibodies against the Bovine Ephemeral Fever Virus (BEFV), however only water buffaloes (*Bubalus bubalis*) and cattle develop clinical illness and BEFV has only been isolated from cattle. Antibodies have been discovered in wild water buffaloes, wild Chitral deer (*Axis axis*), domesticated red deer (*Cervus elaphas*), and feral Rusa deer (*Cervus timorensis*) in Australia. Buffalo populations are large enough to act as a major reservoir of illness in areas of tropical Australia, whereas deer populations are insignificant in number. Antibodies have not yet been tested on deer in Asia and Europe. Natural antibodies have not been found in any horse, marsupials, pigs, sheep, cats, rodents, or dog species (Dinter and Morein 1990). The disease is seasonal, with a higher prevalence during the hot, wet season (rainy season in tropical and subtropical zones, summer and autumn in temperate zones), when conditions favor arthropod vector growth. Intrinsic and extrinsic factors influence an individual's receptivity and sensitivity. The animal's species is one of the individual characteristics that have a considerable impact. Domestic cattle and buffaloes are the primary hosts of three-day sickness. Infected wild ruminants (wildebeest, eland and buffalo) generally display no symptoms. Heavy animals and dairy cattle are more vulnerable to illness and are more likely to succumb to severe variants. In a particular herd, the prevalence of the disease is higher in females than in males, as observed in a study in Iran, and it also increases with age (Momtaz et al. 2012). A warm, wet season, heavy rain; physical exhaustion; low-lying, wet swampy locations; flood plains and irrigated agriculture zones are examples of extrinsic variables (Akakpo 2015). In afflicted regions where the vectors persist all year, three-day fever develops as an enzootic or sporadic disease. In optimal seasons (the rainy season in tropical zones, or summer and fall in temperate zones), the prevalence of arthropod vectors rises. With the onset of less favorable, dry, or cold season, prevalence drops. Morbidity is often severe (50-100%) during epizootic outbreaks, but death is always modest (2-3%). The disease caused 59% morbidity and fewer than 1% fatality when the disease first occurred in Saudi Arabia (Elzein et al. 1997).

Economic Impact

BEF has a significant economic impact, ranging from mortality to trade consequences between and within countries. Because the BEF virus primarily affects the herd's most productive animals, mortality rates for mature cows, bulls, and working oxen are typically lower when expressed as a percentage of the overall herd. A prolonged reduction of body weight, presumably due to fat and muscle loss, is minor, and body weight returns to pre-illness levels, after two weeks following the cure. The percentage of milk production lost varies on an average of 46%, the range is from 34% to 95%. Milk yield did not restore to pre-illness levels after recovery. Females may have some loss due to abortion, while males may experience temporary infertility. Finally, the BEF virus poses a serious threat to both domestic and international animal traffic. It is costly to keep bulls whose sperm will be exported in an insect-proof facility and to regularly monitor for signs of BEF virus infection (Nandi and Negi 1999).
Between 1949 and 1951, roughly 67 thousand cattle were infected with BEF throughout central and southern Japan, resulting in a two billion Japanese yen (in the 1950s, around 5.5 million US dollars) economic loss (Matsumoto 2010). The cost of a BEF outbreak in Israel in 1999 was estimated to be$112 per non-lactating cow and $280 per lactating cow (Walker 2008).

Diagnosis

In field conditions, diagnosis depends upon the epidemiological data, clinical signs and lesions related to the disease. Bovine ephemeral fever is typically suspected in enzootic locations or during the season when arthropod vectors are most active (hot, wet season, low-lying, swampy areas, wet areas, flood, or delta plain) (Bakhshesh and Abdollahi 2015). In a fattening cattle or intense dairy system with better breeds, it should also be suspected if multiple animals concurrently exhibit fever, lameness and limb stiffness, and then recovery occurs quickly. Another strong indicator of the disease is the presence of a sero-fibrinous exudate in the joints. If there are no characteristic clinical symptoms, it is impossible to diagnose the disease in the field with certainty, necessitating the use of laboratory testing to support or reject a clinical diagnosis (Akakpo 2015).
Laboratory diagnosis includes both direct and indirect testing of blood for microbiological testing to detect the virus and specific antibodies during the hyperthermic phase. During the phase of hyperthermia blood collected with anticoagulants

can be used to isolate the virus in a culture and to identify the viral genome. Direct examination can also be done to diagnose the disease (Akakpo 2015).

A blood smear on a slide can be used for histological analysis for immunofluorescence and for counting blood cells. The virus is obtained either by intracerebral inoculation of newborn mice or in a culture of blood leukocytes on cell lines (BHK-21 or Vero). By neutralizing the viral culture in the presence of the right antiserum or by looking for immunofluorescence on the cell lawn, the virus can be identified. This expensive reaction yields a result in three to four days (Akakpo 2015). The traditional reverse transcription polymerase chain reaction (RT-PCR) can be used to determine the viral genome (Zheng et al. 2011).

Prevention and Control

For the control of the disease, restriction of animal movement from infected areas is practiced but the only method to control and prevent the disease is vaccination.

Four types of BEF vaccine have been developed to date: 1. inactivated vaccines; 2. live-attenuated vaccines; 3. recombinant vaccines; and 4. sub-unit G protein-based vaccines. The field uses live-attenuated, inactivated, and subunit vaccinations. South Africa, Australia, Japan, Namibia, South Korea, Taiwan, Philippines, mainland China, Turkey, Kuwait, Israel, Oman, Saudi Arabia, Bahrain, and Egypt have all adopted vaccination to varied degrees. The source virus from which the vaccines are made, the process used for attenuation or inactivation, and the adjuvant formulation vary between the vaccinations. Most vaccines' protective immunity seems to have a short half-life, which could make them ineffective unless further booster doses are given at intervals of six months to a year. Further investigation is still required to provide a more thorough assessment of performance in the field and to assess slow-release and other cutting-edge technologies that might decrease the number of doses needed and lengthen the duration of protection (Walker and Klement 2015). Eliminating arthropod vectors and establishing animal hygiene practices are the cornerstones of infection prevention strategies. Results are variable, particularly in nations where vector control programs fall short of expectations and livestock husbandry is mostly pastoral (Akakpo 2015).

Treatment

The virus that causes bovine ephemeral fever has no specific treatment. However, the symptoms are treatable, and hygiene precautions can be taken. Nonsteroidal anti-inflammatory medicines, such as IM or IV flunixin meglumine (2.2 mg/kg/day) or IM ketoprofen (3 mg/kg/day), are used as palliative care to relieve symptoms without altering the course of the disease. For three days, all therapies are continued. Although phenylbutazone may be the most efficient treatment, the frequency of injections is impracticable and raises questions about slaughter residue. In several nations, the use of phenylbutazone in cattle is also prohibited. Cows exhibiting hypocalcemia symptoms should receive parenteral treatment with calcium borogluconate and according to field observations, parenteral treatment with calcium solutions frequently aids in helping a cow that is staying stand up. The recumbent animal must be properly fed (Constable et al. 2016).

Hygiene practices are used to prevent or correct conditions that help spread the disease. Resting ill animals is crucial since, in a pasture system, if they seek for water or food, the clinical indications may worsen and the mortality rate may rise. Animals who are recovering from illness need to be properly nursed in order get recovery soon (Akakpo 2015).

Conclusion

BEF is a viral illness of food animals and has a significant economic impact due to its epidemiology. This disease is very important since the virus has unique virology and replication properties. Animals are given vaccines as a kind of prevention when they are developed. There is no known cure for BEF virus. Anorexia, stiffness and lameness are the symptoms mostly appeared. In palliative care, nonsteroidal anti-inflammatory drugs are utilized. Since sick animals need to be nurtured, resting them is essential.

REFERENCES

Abu Elzein EM et al., 1999. Observations on the Recent Epizootic of Bovine Ephemeral Fever in Saudi Arabia. Revue Scientifique et Technique 18(3): 672-680. https://doi.org/10.20506/rst.18.3.1188

Akakpo AJ, 2015. Three-Day Fever: Revue Scientifique et Technique. 34(2): 525-538.

Aziz-Boaron O et al., 2012. Circulation of Bovine Ephemeral Fever in the Middle East—Strong Evidence for Transmission by Winds and Animal Transport. Veterinary Microbiology 158(3): 300-307. https://doi.org/https://doi.org/10.1016/j.vetmic.2012.03.003

Bai WB, 1991. Preliminary Observations on the Epidemiology of Bovine Ephemeral Fever in China. Tropical Animal Health Production 23(1): 22-26. https://doi.org/10.1007/bf02361265

Bakhshesh M and Abdollahi D, 2015. Bovine Ephemeral Fever in Iran: Diagnosis, Isolation and Molecular Characterization. Journal of Arthropode Borne Diseases 9: 195-203.

Chaisirirat T et al., 2018. Molecular Characterization of Bovine Ephemeral Fever Virus in Thailand between 2013 and 2017. Veterinary Microbiology 227: 1-7. https://doi.org/10.1016/j.vetmic.2018.10.013

Constable P et al., 2016. Veterinary Medicine: A Textbook of the Diseases of Cattle, Horses, Sheep, Pigs and Goats.

Daniels PW et al., 1995. Australian-Indonesian Collaboration in Veterinary Arbovirology--a Review. Veterinary Microbiology 46(1-3): 151-174. https://doi.org/10.1016/0378-1135(95)00080-t

Dinter Z and Morein B, 1990. Virus Infections of Ruminants: Virus Infections of Vertebrates Series (Vol. 3). Elsevier.

Elzein E at al., 1997. Bovine Ephemeral Fever in Saudi Arabia. The Veterinary record 140: 630-631. https://doi.org/10.1136/vr.140.24.630

El-Nesr K et al., 2010. Bovine Ephemeral Fever: Pathological and Immunohistochemical Studies. Journal of Veterinary Medical Research 20: 63-68. https://doi.org/10.21608/jvmr.2020.77581

Feray Alkan HA, 2017. Assessment of the Molecular Epidemiology of Bovine Ephemeral Fever in Turkey. Veterinarski Arhiv 87(6): 665-675. https://doi.org/10.24099/vet.arhiv.160711

George and Standfast, 2019. "Bovine ephemeral fever." The arboviruses: epidemiology and ecology. CRC Press, 71-86.

Hirashima Y et al., 2017. Resurgence of Bovine Ephemeral Fever in Mainland Japan in 2015 after a 23-Year Absence. Journal of Veterinary Medical Science 79(5): 904-911. https://doi.org/10.1292/jvms.16-0345

Hsieh YC, 2005. Bovine Ephemeral Fever in Taiwan (2001-2002). The Journal of Veterinary Medical Science 67(4): 411-416. https://doi.org/10.1292/jvms.67.411

Lapira JEE, 2018. Molecular Detection of Ephemeral Fever Virus among Large Ruminants in the Philippines. Virusdisease 29(3): 400-404. https://doi.org/10.1007/s13337-018-0468-y

Lee F, 2019. Bovine Ephemeral Fever in Asia: Recent Status and Research Gaps. Viruses 11(5). https://doi.org/10.3390/v11050412

Matsumoto K, 2010. History of Pandemic Influenza in Japan. Nihon Rinsho 68(9): 1595-1601.

Maclachlan N et al., 2016. Fenner's Veterinary Virology: Fifth Edition.

Mullen GR et al., 2009. Medical and veterinary entomology. Academic press.

Mirzaie K et al., 2017. Determinants of Bovine Ephemeral Fever Outbreak During 2013, in Qazvin Province, Iran. Asian Pacific Journal of Tropical Disease 7: 744-747.

Momtaz H et al., 2012. Molecular Epidemiology of Bovine Ephemeral Fever Virus in Cattle and Buffaloes in Iran. Revue de Medecine Veterinaire 163: 415-418.

Nandi S and Negi B, 1999. Bovine Ephemeral Fever: A Review. Comparitive Immunology and Microbiology Infectious Diseases 22(2): 81-91.

St George TD, 1992. The Natural History of Ephemeral Fever of Cattle. Proceedings of the 1st International Symposium on Bovine Ephemeral Fever and Related Rhabdoviruses, Beijing.

St George TD, 1997. Effective treatment of bovine ephemeral fever. Australian veterinary journal 75(3): 221–223. https://doi.org/10.1111/j.1751-0813.1997.tb10074.x

Sayed-Ahmed M, 2005. Some Studies On Bovine Ephemeral Feve Thesis presented (Doctoral dissertation, Mansoura University).

Taghipour Bazargani T et al., 2013. Identification of Bovine Ephemeral Fever (Bef) Outbreak in a Large Dairy Farm in Varamin, Iran. Iranian Journal of Veterinary Science and Technology 5(1): 35-44. https://doi.org/10.22067/veterinary.v5i1.26529

Tonbak S et al., 2013. A Large-Scale Outbreak of Bovine Ephemeral Fever in Turkey, 2012. The Journal of Veterinary Medical Science 75(11): 1511-1514. https://doi.org/10.1292/jvms.13-0085

Uren M. F et al., 1992. Studies on the pathogenesis of bovine ephemeral fever in experimental cattle III. Virological and biochemical data. Veterinary Microbiology, 30(4), 297-307.

Walker PJ, 2008. Bovine Ephemeral Fever Virus, 3rd Ed., Encyclopedia of Virology, Academic Press, Cambridge, Massachusetts. https://doi.org/https://doi.org/10.1016/B978-012374410-4.00767-6

Walker PJ, 2005. Bovine ephemeral fever in Australia and the world. The World of Rhabdoviruses 57-80.

Walker PJ and Klement E, 2015. Epidemiology and Control of Bovine Ephemeral Fever. Veterinary Research 46(1): 1-19.

Wang FI et al., 2001. Bovine Ephemeral Fever in Taiwan. Journal of Veterinary Diagnostic Investigation 13(6): 462-467. https://doi.org/10.1177/104063870101300602

Yang D et al., 2018. Analysis of Five Arboviruses and Culicoides Distribution on Cattle Farms in Jeollabuk-Do, Korea. Korean. Journal of Parasitology 56(5): 477-485. https://doi.org/10.3347/kjp.2018.56.5.477

Yeruham I et al., 2010. Epidemiological Investigation of Bovine Ephemeral Fever Outbreaks in Israel. Veterinary Internal Medecine https://doi.org/10.4061/2010/290541

Zahid M et al., 2019. Seromolecular Prevalence of Befv Antibodies, Their Correlation with Physiological Biomarkers and Identification of Risk Factors under Field Conditions. Pakistan Journal of Zoology 51(1): 205-210.

Zheng F and Qiu C, 2012. Phylogenetic Relationships of the Glycoprotein Gene of Bovine Ephemeral Fever Virus Isolated from Mainland China, Taiwan, Japan, Turkey, Israel and Australia. Virology Journal 9: 268. https://doi.org/10.1186/1743-422x-9-268

Zheng F et al., 2011. A Reverse- Transcription, Loop-Mediated Isothermal Amplification Assay for Detection of Bovine Ephemeral Fever Virus in the Blood of Infected Cattle. Journal of Virological Methods 171(1): 306-309. https://doi.org/10.1016/j.jviromet.2010.10.028

Epidemiology of Influenza Viruses

AUTHORS DETAIL

Mehroz Latif[1*], Muhammad Umar Hayat[1], Muhammad Hassan Rehman[1], Muhammad Irfan Anwar[2], Sehrish Gul[3], Mehvish Parveen[4], Namra Mariam[3]and Muhammad Danial[1]

[1]Faculty of Veterinary Sciences, Bahauddin Zakariyya University, Multan
[2]Department of Pathobiology, Faculty of Veterinary Sciences, Bahauddin Zakariyya University, Multan
[3]Institute of Microbiology, University of Agriculture, Faisalabad
[4]Department of Biosciences, COMSATS University Islamabad
*Corresponding author: mehrozlatif3321@gmail.com

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INTRODUCTION

Each year, influenza viruses cause 3-5 million infections of the respiratory system and almost 250,000–500,000 severe cases (Kreijtz et al. 2011). Once within the host's body, the influenza virus can attack any organ and cause an acute sickness with varying degrees of respiratory and systemic symptoms. The virulence of the viral strain and the degree of animal immunity prior to the pandemic determine the severity of the illness (Krammer et al. 2018).

Etiology

The influenza viruses belongs to the Orthomyxoviridae family, have negative-sense, single-stranded, segmented RNA genomes, and are responsible for influenza infliction in animals (Taubenberger and Morens 2008). Influenza viruses come in three main subtypes: A, B, and C. They are all members of various host ranges. Influenza Virus A has been isolated from numerous animals, including humans, pigs, horses and a variety of domestic and wild birds, Influenza Virus B and C solely harm humans (Fouchier et al. 2003). The Type D virus, a close relative of the Type C virus, was discovered in cattle, sheep, and goats after being first discovered in pigs in 2011. (Ferguson et al. 2016). There is no evidence that Type D viruses infect people (Foni et al. 2017). The different subtypes of Influenza Virus type A are based on the presence of the hemagglutinin (HA) and neuraminidase (NA) membrane glycoproteins: 18 HA types (H1→ H18) and 11 NA (N1→ N11) (Henritzi et al. 2019). The influenza viruses that infect both mammalian and non-mammalian species are thought to descend from the avian virus (Sreenivasan et al. 2018). The influenza virus attaches and enters the host's cell membranes to infect the host. The virus enters these cells by attaching to cell surface receptors through HA (Byrd-Leotis et al. 2017). NA facilitates viral replication and permits virus discharge from the host cell (Shtyrya et al. 2009).

Epidemiology

In temperate areas of the northern and southern hemispheres, seasonal epidemics frequently happen in the winter (Tamerius et al. 2011). However, in tropical areas, influenza outbreaks can happen at any time of year (Sagripanti and Lytle 2007). It has been demonstrated that the influenza virus A can infect a wide range of animal species. In terms of the epidemiology of influenza, pigs and horses appear to be more significant than humans and birds. Compared to humans, the sickness in pigs causes substantial morbidity but low mortality (Brown 2000).

Canine Influenza Virus (CIV) subtype H3N8 was initially identified in racing greyhounds in 2004. (Crawford et al. 2005). There have been rare reports of additional CIV-H3N8 illnesses in other parts of the world, including Canada, the United Kingdom, Australia, China, and Nigeria, but there is no proof that the virus is still spreading in these places (Kruth et al. 2008). CIV-H3N2 subtype was reported in China and South Korea in 2006, and it was then spread to several South-East Asian countries (Li et al. 2010). The disease infected more than 1000 canines in Chigago, US, in 2015, marking the country's first detection of this nature (Voorhees et al. 2017). Cats in New York City were found to be infected with CIV-H7N2 in December 2016. During this outbreak, there were also reports of cat-to-human transmission (Belser et al. 2017). Direct contact with diseased birds, especially through eating raw poultry, has resulted in the infection of dogs and cats (Borland et al. 2020).

Equine influenza is a clinical disease of horses, donkeys and mules that is common throughout the world and main culprit behind it are influenza A viruses of subtypes H7N7 and H3N8 (Cullinane and Newton 2013). Since there have been no reports of virus isolation from horses since 1980, it's possible that subtype H7N7 viruses have vanished from the population of horses (Webster 1993). Except for New Zealand, outbreaks of equine influenza are widespread everywhere. Outbreaks were caused by the importation of

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subclinical infected horses in India (1987), Hong Kong (1992) and Australia (2007) (Mumford 1993; Powell et al. 1995; Cowled et al. 2009). During these epidemics, the virus spread through the movement of horses following horse exhibitions, sales, racing meets, and other events. This occurred in the United Kingdom in 1979 and in Ireland in 1989, when the Influenza virus emerged from these events (Burrows et al. 1981; Van Maanen and Cullinane 2002). The mortality rate for equine influenza is typically low, although young foals without maternal antibodies have died from the disease (Patterson-Kane et al. 2008). Equine influenza broke out in northeastern China in 1989, with a fatality rate of up to 20% (Gorman et al. 1991). In Europe, the first known epidemic occurred between 1173 and 1174, and the first pandemic for which a general agreement was signed occurred in 1580. The 1889 epidemic marked the start of modern influenza epidemiology. During the 1918-19 pandemic, an H1N1-like virus related to a virus identified in pigs caused "the greatest medical genocide in history," killing up to one-hundredth of the world's population (Shortridge 1999). Since influenza viruses can spread between different species, an outbreak of canine influenza in 2007 led to the outbreaks in North America, England and Australia. There is no proof that the equine influenza virus spreads from dogs to horses, even though interspecies transmission of the virus from horses to dogs has been proven (Yamanaka et al. 2009; Yamanaka et al., 2012).

Pathogenesis

There are two ways that the influenza virus can influence the respiratory system; 1- directly attacking the respiratory system or 2- affecting an animal's immune system (Kalil and Thomas 2019). Virus enters the body and begins to develop. The incubation period is influenced by the virus's virulence and immunity. In horses, it could last as little as 24 hours (Cullinane and Newton 2013).

The body is invaded by a virus, which destroys the ciliated respiratory epithelium and lowers the tracheal clearance rate (Willoughby et al. 1992). The cleavage of sialic acid from mucus by neuraminidase contributes to the virus's improved motility. Due to this cleavage, the horse's defenses against opportunistic infections may be weakened. The virus typically caused bronchial epithelial necrosis by replicating in the upper and lower respiratory tracts (Cullinane and Newton 2013). Squamous metaplasia, epithelial necrosis, and intraluminal necrotic debris can be detected upon histological inspection (Patterson-Kane et al. 2008).

Clinical Signs

Equine influenza virus infections typically have a severe, dry, explosive, non-productive and persistent cough. The host's immunity, the virus's virulence, and the dosage all affect the severity of infection. Fever may occasionally be present.

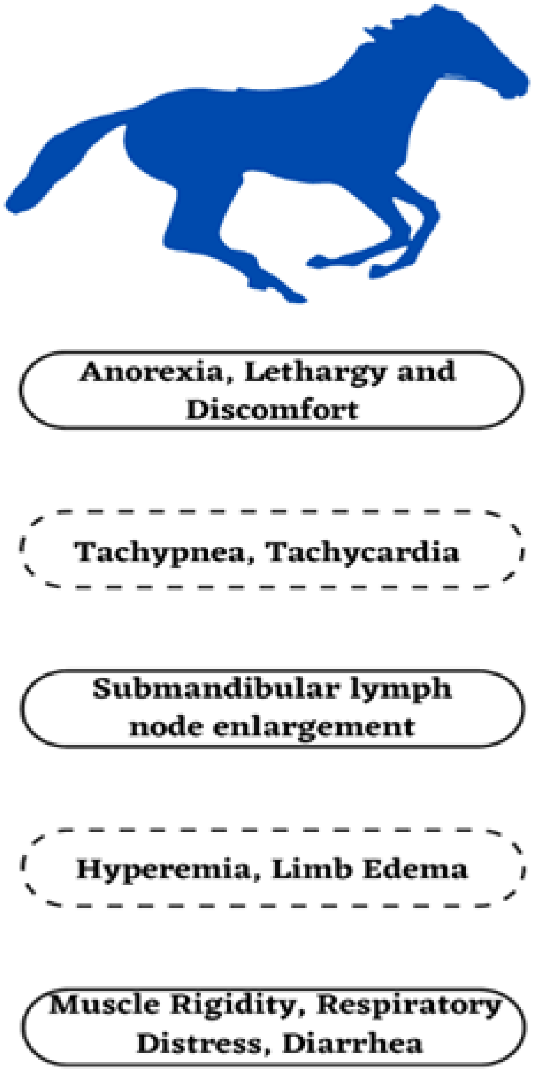
Anorexia, Lethargy and Discomfort
Tachypnea, Tachycardia
Submandibular lymph node enlargement
Hyperemia, Limb Edema
Muscle Rigidity, Respiratory Distress, Diarrhea

Fig. 1: Clinical Signs of Equine Influenza

A subsequent bacterial infection may manifest as mucopurulent discharge and wheezes or crackles. There may be signs of anorexia, lethargy, discomfort and very rarely, submandibular lymph node enlargement. When eating, irritated airways might cause coughing and gagging. Inspiratory and expiratory bronchovesicular noises become more intense. In addition to being depressed and intolerant of activity, the animal may also develop valvular insufficiency and congestive heart failure in extreme circumstances. Tachypnea, tachycardia, hyperemia, limb edema and muscle rigidity are other symptoms that are frequently observed (Fig. 1). In extreme circumstances, there may be hard breathing, reluctance to move, and other respiratory distress symptoms. In most cases, the influenza virus is not associated with diarrhea, but enteritis has been noted to be a common symptom in horses in Northern China (Abdelwhab and Abdel-Moneim 2019).

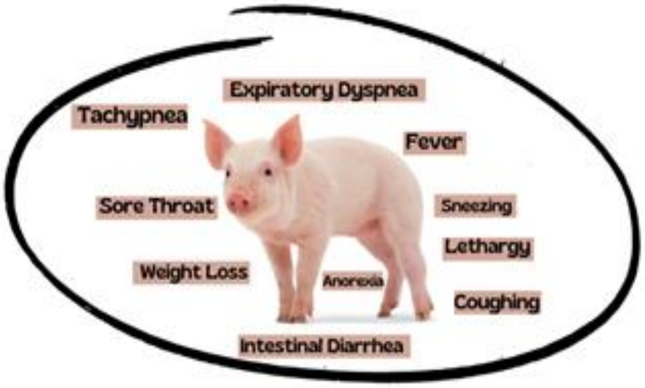

Fig. 2: Clinical Signs of Swine Influenza

An acute infection called swine influenza is passed from pigs to pigs. Infected pigs exhibit fever, lethargy, anorexia, tachypnea, and expiratory dyspnea within two days of infection (Fig. 2). Bronchitis-related deep barking cough on day three and four may be present. Later, the fever drops and pregnant animals may abort. Pigs recover swiftly in the absence of subsequent bacterial infections (Janke 2013).

Clinical symptoms for canine influenza virus are not pathognomonic. The dogs typically exhibit anorexic and lethargic symptoms along with nasal discharge. Clear nasal discharge eventually turns mucopurulent with time. A dry, persistent cough that produces no results can last for a few weeks. Kennel cough and CIV infection are difficult to distinguish from one another (Dubovi and Njaa 2008).

Avian Influenza Viruses

Avian Influenza Viruses (AIVs) are the precursors of human influenza type A virus. Prior to infecting human hosts, they can spread through bird reservoirs or by infecting mammalian species (Reperant et al. 2012). Infections with the avian influenza virus typically have low virulence (low pathogenicity) in birds and have little to no negative health effects. However, the AIV subtypes H5 and H7 have the potential to develop virulence-enhancing mutations in the HA gene, leading to highly pathogenic (HP) viruses that can quickly wipe out flocks of chicken (EM Abdelwhab et al. 2014).

A wide variety of wild and domestic bird species have been shown to carry avian influenza viruses (AIVs), but their natural reservoirs are the wild waterbirds of the orders Anseriformes and Charadriformes, such as ducks, geese, swans and shorebirds (Venkatesh et al. 2018). For many years, avian influenza viruses (AIVs) have posed a serious risk to the general public's health. AIV subtypes H5, H6, H7, H9 and H10 cause at least five of the human infections in China. The ongoing development of AIVs could result in the emergence of potentially dangerous and highly contagious AIV variants among populations of humans (Qi et al. 2018).

Etiology

Avian influenza viruses are Type A orthomyxoviruses, also known as Alpha influenza viruses. Almost, 16 haemagglutinin (H1-16) and 9 neuramanidase (N1-9) subtypes of AI viruses have been identified so far (Leyson et al. 2019). Recently, human illnesses and deaths have been linked to the avian influenza virus subtypes H7N9 and H10N8, which have low pathogenicity for poultry. The H9N2 strain has been isolated from domestic and wild avian species across the world for several decades, but because of its low pathogenicity to poultry and low priority for animal disease prevention, it has been able to continue to mutate and spread. H9N2 influenza viruses have been isolated from both domestic and wild bird species over the past few decades. In mice, the viruses have been demonstrated to proliferate without prior adaption (Li et al. 2014).

Epidemiology

In Asia, the first low-pathogenic avian influenza virus (LPAIV) was H9N2, and the first high-pathogenic avian influenza virus (HPAIV) was H5N1, which emerged in Guangdong Province, China, in 1994 and 1996, respectively. Currently, the most common AIV subtypes in China are H9 and H5, which are present in many regions. Both chicken farms with and without vaccinations have a high prevalence of H9N2 and H5N1, which frequently result in isolated outbreaks (Su et al. 2015).

The highly virulent H5N1 avian influenza subtype was first detected in Egypt in 2006 and the country was officially declared enzootic in 2008. H5N1 infections have recently been seen in high numbers in humans and poultry birds. The analysis of surveillance data from 2009 to 2014 demonstrates that AIVs are well-established in Egyptian poultry and are undergoing genetic and antigenic evolution (Kayali et al. 2016). The dealing of parrots altered the temporal trend of global parrot trade volumes and the geographic distribution of trade hubs over the previous 42 years (1975–2016), which led to the emergence of pandemic zoonoses, such as the H5N1 avian influenza (Lai et al.2016). Highly pathogenic avian influenza viruses (HPAIV) caused serious outbreaks in Germany and Europe in the autumn/winter of 2016–2017 and 2020–2021. Increased wild bird mortality along with significant losses in the poultry industry were caused by many subtypes (Bodewes et al. 2018).

Due to avian influenza epidemics, about 400 million birds have been killed worldwide since 2003. Highly pathogenic avian influenza viruses can develop from LPAIVs that are currently circulating in poultry (HPAIVs). In Bangladesh's Netrokona district between June and July 2011, 61% (1789/2930) of chickens, 47% (4816/10 184) of ducks, and 73% (358/493) of geese died because of the influenza virus infection (Haider et al. 2017). Mortality rates from the H9N2 influenza virus surged from 2% to 15% in the Moroccan towns of Fez, Meknes, Kenitra and Rabat, which led to a decrease in egg production in the second week of January 2016 (El Houadfi et al. 2016).

Pathogenesis

LPAIV infection in birds replicates in the intestinal tract and, in lower titers in the respiratory tract (Kida et al. 1980; Van Dijk et al. 2015). Following spillover into poultry, LPAIV subtypes H5 and H7 may develop into HPAIV, which is fatal for poultry and may occasionally result in illness and death in humans and wild birds (Alexander 2007). AIVs are essential for receptor attachment and recognition. Viruses HA is the key factor in determining host range. The HA of avian influenza viruses is selective for SA receptors located in the bird's digestive system (Shao et al. 2017). The disease syndrome in birds ranges from preclinical to mild upper respiratory sickness. The loss of egg production results due to the highly contagious and rapidly growing systemic disease that causes major epidemics with extremely high morbidity and mortality in the affected poultry flocks. The incubation period of virus ranges from a few hours to three days (Alexander 2000; Dhama et al. 2005; Capua and Alexander 2009).

Clinical Signs

After 3 to 7 days of inoculation, birds with AIV infection display clinical signs i.e., coughing, ocular and nasal discharge, and conjunctivitis. Birds may die on day 3 and 5 after HPAI infection due to bleeding and numerous organ necrosis. In addition to myocarditis, hepatitis, splenitis, interstitial pneumonia, nephritis, and hyalinization to necrosis of skeletal myofibers, HPAI induces multifocal necrosis in several visceral organs (Fig. 3). According to a study, the brains of infected ducks also showed moderate lesions, which were characterized by perivascular lymphoplasmacytic cuffs around a few localized cerebral vessels and associated small foci of gliosis (Zhao et al. 2012).

Human Influenza Viruses

Although the influenza virus has been detected in different species, it may rarely and infrequently infect humans. Few incidences of zoonotic disease were noticed in China in 2013, and many reports were immiscible. However, no other occurrence in humans were documented after that until 2019 (Chen et al. 2022). The influenza virus subtypes H5N1, H5N6, H7N9, and H9N2 can infect mammals and have reported to cause a total of 2000 illnesses in humans (Wang et al. 2020). Between 1959 to 2021, there were almost 707 reported cases of influenza virus in humans with low intensity (Chen et al. 2022). About 5–10% of adults and 20–30% of children have been infected with influenza virus infection. Around 1,145,278 cases of influenza were reported in China during the outbreak in 2020, and there were 70 reported fatalities (Wang et al. 2022).

Coughing, Ocular and Nasal Discharge & Conjunctivitis
Multifocal necrosis in visceral organs & skeletal myofibrils.
Perivascular lymphoplasmacytic cuffs around cerebral vessels

Fig. 3: Clinical Signs of Avian Influenza in ducks

According to numerous investigations, there were three waves of direct human-to-human transmission that involved 133 persons, with 68 deaths in Vietnam, Thailand, Cambodia, Indonesia, and China (Wong and Yuen 2006). In 2011, there was influenza D virus outbreak in the United States and Canada with 1.3% seroprevalence rate (Hause et al. 2013). It was reported that in the influenza outbreak of Florida, 94% of cattle-contact employees had IDV infection (Trombetta et al. 2019). According to reports, there has been a substantial rise in the seroprevalence of the influenza D virus in Italy i.e., 5% in 2005 to 46% in 2014 (Vega-Rodriguez and Ly 2023).
Influenza infections in human is typically caused by the H5N1 strain which damages the alveolar macrophages and epithelial cells (Hui et al. 2009). When the alveolar barrier is damaged, it can result in several respiratory tract issues, including severe pneumonia (Wonderlich et al. 2017). It may also cause cardiac issues in people by interfering with the angiotensin-converting enzyme system (Wu et al. 2022).
Infection with the influenza virus in humans is typically accompanied by pancytopenia, elevated liver enzymes, renal failure, and gastrointestinal symptoms. Lower respiratory tract involvement and a low total peripheral white blood cell count or lymphopenia may result from negligence and delayed hospitalization (Yuen et al. 1998). The clinical symptoms of infection i.e., fever, sore throat, chills, and nasal discharge, are typically modest. The symptoms vanished after one week of infection with no pneumonia (Yang et al., 2022). The H5N6 influenza strain can cause mild pneumonia and acute encephalitis. Multiple neurological signs may also be seen that can result in seizures and coma (Zhang et al. 2022).

Diagnosis

The diagnosis is typically made using clinical indicators that are correlated with laboratory results, epidemiological data, and disease symptoms (Binnicker et al. 2015). Before laboratory confirmation, fever and cough are the two most important signs that indicate an influenza infection (Anderson et al. 2018). The diagnostic techniques for finding the influenza virus are as follows:

- Rapid influenza diagnostic methods are mainly immunoassays that detects subtype A and B from throat, nasopharyngeal, and nasal swab in less than 30 min. It displays the result qualitatively (positive vs. negative). It has high specificity, and false-positive results from the tests are attributed to lower infection activity (Trombetta et al. 2018).
- Reverse transcriptase PCR (RT-PCR) assay detects subtype A and B from throat swab, nasopharyngeal swab, nasal aspirate, and sputum in less than 80 min. It helps in diagnosing its subtypes and detecting anti-viral resistance (Vemula et al. 2016).
- Nucleic acid amplification tests detect A and B subtypes from nasopharyngeal swab in less than 30 min (Javanian et al. 2021).
- Culturing detects subtype A and B from throat swab, nasal swab and wash sputum. It takes a time of minimum 3 days. The culturing helps in strain typing and leads to the specific diagnosis of influenza infection (Leland and Ginocchio 2007).

Electrolyte levels, thrombocytopenia, and a complete blood count are non-specific diagnostic tests for influenza virus (Javanian et al. 2021).

Vaccination

In addition to management and simple preventive measures, vaccination is one of the most effective strategies (Nishiura and Satou 2010). The first equine influenza vaccinations with inactivated virus were introduced in the 1960s (Paillot 2014). Equine influenza vaccinations come in three different forms: entire inactivated, live-attenuated, and viral-vector based (Paillot 2014). Except for the live attenuated EI vaccine, naive horses must have a primary course of two immunizations spaced four to six weeks apart, a third booster dose five to six months later, and then biannual or annual immunizations in accordance with the product recommendation (Woodland 2013).

The Swine Influenza Virus constantly shifts its antigenic makeup. The current inactivated SIV vaccine production and licensing method is unable to cope the drift. Only inactivated whole-virus vaccinations are now commonly utilized to prevent swine influenza around the world (Ma and Richt 2010).

There is a CIV vaccination approved by the US Department of Agriculture in the country. A H3N2 vaccination with an avian origin was also developed in Korea. Both vaccinations contain viruses that have been killed as adjuvants. Although yearly vaccines for dogs are advised, despite the lack of information regarding the durability of immunity (Dubovi 2010).

Treatment

Rest in a well-ventilated area is a crucial part of animal treatment. The time required for the damaged and necrosed epithelia to fully heal will be provided by the rest. In most cases, the treatment is symptomatic and involves giving the animal adequate nursing care, clean water in sufficient quantities to avoid dehydration, palatable feed and dust-free, dry bedding. Therapy with antibiotics and anti-inflammatory drugs can be started as needed. As the cleansing and protecting function for emptying the secretions, coughing shouldn't be inhibited. Animals' immune systems can also be strengthened using immune stimulants. Antiviral treatments like amantadine and rimantadine can be used, although they are expensive for routine use (Van Maanen and Cullinane 2002).

Control and Prevention

To stop the disease from spreading, the following preventative actions should be implemented:

- The risk of influenza infection is decreased by isolation, quarantine and clinical monitoring of new animals in the herd.
- Prevent animals from congregating in a single air space.
- Adoption of strict biosecurity controls to prevent the spread of disease by workers and contaminated vehicles (Gildea et al. 2011).
- The preventative measure, together with the surveillance system, is vaccination. Programs for strain characterization and surveillance are essential for controlling influenza with vaccination (Cullinane et al. 2010).
- The most effective way to limit the morbidity and mortality in humans by avian influenza viruses is through increased public awareness, especially in underdeveloped areas. A team of professionals should be established for surveillance and to take precautions on time (Sendor et al. 2022).

Conclusion

Animals and humans can acquire influenza, which is a contagious disease, but it can be avoided with immunization, proper management practices, and biosecurity measures. It can cause significant financial losses, which is very concerning for health professionals and veterinarians around the world. Along with serious complications, it may also result in secondary bacterial infections. To address the condition properly, a differential diagnosis must be done. For the eradication of outbreaks from society, influenza surveillance must also be conducted with extreme care.

REFERENCES

Abdelwhab EM and Abdel-Moneim AS, 2019. Orthomyxoviruses. In: Malik YS, editor. Recent advances in animal virology: Springer, Singapore; pp: 351-378.

Abdelwhab EM et al., 2014. Prevalence and control of H7 avian influenza viruses in birds and humans. Epidemiology and Infection 142(5): 896-920.

Alexander DJ, 2000. A review of avian influenza in different bird species. Veterinary Microbiology 74(1-2): 3-13.

Alexander DJ, 2007. An overview of the epidemiology of avian influenza. Vaccine 25(30): 5637-5644.

Anderson KB et al., 2018. Clinical and laboratory predictors of influenza infection among individuals with influenza-like illness presenting to an urban Thai hospital over a five-year period. PLoS One 13(3): e0193050.

Belser JA et al., 2017. A novel A (H7N2) influenza virus isolated from a veterinarian caring for cats in a New York City animal shelter causes mild disease and transmits poorly in the ferret model. Journal of Virology 91(15): e00672-17.

Binnicker MJ et al., 2015. Direct detection of influenza A and B viruses in less than 20 minutes using a commercially available rapid PCR assay. Journal of Clinical Microbiology 53(7): 2353-2354.

Bodewes IL et al., 2018. Systemic interferon type I and type II signatures in primary Sjögren's syndrome reveal differences in biological disease activity. Rheumatology 57(5): 921-930.

Borland S et al., 2020. Influenza A virus infection in cats and dogs: a literature review in the light of the "one health" concept. Frontiers in Public Health 8: 83.

Brown IH, 2000. The epidemiology and evolution of influenza viruses in pigs. Veterinary Microbiology 74(1-2): 29-46.

Burrows R et al., 1981. Field and laboratory studies of equine influenza viruses isolated in 1979. The Veterinary Record 109(16): 353-356.

Byrd-Leotis L et al., 2017. The interplay between the host receptor and influenza virus hemagglutinin and neuraminidase. International Journal of Molecular Sciences 18(7): 1541.

Capua I and Alexander DJ, 2009. Avian influenza and Newcastle disease: a field and laboratory manual, Springer Science and Business Media.

Chen Y et al., 2022. Poultry to human passport: cross-species transmission of zoonotic H7N9 avian influenza virus to humans. Zoonoses.

Cowled B et al., 2009. The equine influenza epidemic in Australia: spatial and temporal descriptive analyses of a large propagating epidemic. Preventive Veterinary Medicine 92(1-2): 60-70.

Crawford PC et al., 2005 Transmission of equine influenza virus to dogs. Science 310(5747): 482-485.

Cullinane A and Newton JR, 2013. Equine influenza—A global perspective. Veterinary Microbiology 167(1-2): 205-214.

Cullinane A et al., 2010. Equine influenza–surveillance and control. Influenza and other Respiratory Viruses 4(6): 339-344.

Dhama K et al., 2005. Avian influenza: the current perspectives. Journal of Immunology and Immunopathology 7(2): 1-33.

Dubovi EJ and Njaa BL, 2008. Canine influenza. Veterinary Clinics of North America: Small Animal Practice 38(4): 827-835.

Dubovi EJ, 2010. Canine influenza. Veterinary Clinics: Small Animal Practice 40(6): 1063-1071.

El Houadfi M et al., 2016. First outbreaks and phylogenetic analyses of avian influenza H9N2 viruses isolated from poultry flocks in Morocco. Virology Journal 13(1): 1-7.

Ferguson L et al., 2016. Pathogenesis of influenza D virus in cattle. Journal of Virology 90(12): 5636-5642.

Foni E et al., 2017. Influenza D in Italy: towards a better understanding of an emerging viral infection in swine. Scientific Reports 7: 11660.

Fouchier RA et al., 2003. Animal influenza virus surveillance. Vaccine 21(16): 1754-1757.

Gangurde H et al., 2011. Swine influenza A (H1N1 virus): A pandemic disease. Systematic Reviews in Pharmacy 2(2): 110.

Gildea S et al., 2011. Management and environmental factors involved in equine influenza outbreaks in Ireland 2007–2010. Equine Veterinary Journal 43(5): 608-617.

Gorman OT et al., 1991. Evolution of influenza A virus nucleoprotein genes: implications for the origins of H1N1 human and classical swine viruses. Journal of Virology 65(7): 3704-3714.

Haider N et al., 2017. Unusually high mortality in waterfowl caused by highly pathogenic avian influenza A (H5N1) in Bangladesh. Transboundary and Emerging Diseases 64(1): 144-156.

Hause BM et al., 2013. Isolation of a Novel Swine Influenza Virus from Oklahoma in 2011 Which is Distantly Related to Human Influenza C Viruses. PLoS Pathogens 9(2): e1003176.

Henritzi D et al., 2019. A newly developed tetraplex real-time RT-PCR for simultaneous screening of influenza virus types A, B, C and D. Influenza and other Respiratory Viruses 13(1): 71-82.

Hui KPY et al., 2009. Induction of proinflammatory cytokines in primary human macrophages by influenza a virus (H5N1) is selectively regulated by IFN regulatory factor 3 and p38 MAPK. Journal of Immunology 182: 1088–1098.

Janke BH, 2013. Clinicopathological features of swine influenza. Swine Influenza 2013: 69-83.

Javanian M et al., 2021. A brief review of influenza virus infection. Journal of Medical Virology 93(8): 4638-4646.

Kalil AC and Thomas PG, 2019. Influenza virus-related critical illness: pathophysiology and epidemiology. Critical Care 23(1): 1-7.

Kayali G et al., 2016. Avian influenza A (H5N1) virus in Egypt. Emerging Infectious Diseases 22(3): 379.

Kida HI et al., 1980. Duck influenza lacking evidence of disease signs and immune response. Infection and Immunity 30(2): 547-553.

Krammer F et al., 2018. Influenza (primer). Nature Reviews: Disease Primers 4(1): 3.

Kreijtz JH et al., 2011. Immune responses to influenza virus infection. Virus Research 162(1-2): 19-30.

Kruth SA et al., 2008. Seroprevalence of antibodies to canine influenza virus in dogs in Ontario. The Canadian Veterinary Journal 49(8): 800.

Lai S et al., 2016. Global epidemiology of avian influenza A H5N1 virus infection in humans, 1997–2015: a systematic review of individual case data. The Lancet Infectious Diseases 16(7): e108-e118.

Leland DS and Ginocchio CC, 2007. Role of cell culture for virus detection in the age of technology. Clinical Microbiology Reviews 20(1): 49-78.

Leyson C et al., 2019. Pathogenicity and genomic changes of a 2016 European H5N8 highly pathogenic avian influenza virus (clade 2.3. 4.4) in experimentally infected mallards and chickens. Virology 537: 172-185.

Li S et al., 2010. Avian-origin H3N2 canine influenza A viruses in Southern China. Infection, Genetics and Evolution 10(8): 1286-1288.

Li X et al., 2014. Genetics, receptor binding property, and transmissibility in mammals of naturally isolated H9N2 Avian Influenza viruses. PLoS Pathogens 10(11): e1004508.

Ma W and Richt JA, 2010. Swine influenza vaccines: current status and future perspectives. Animal Health Research Reviews 11(1): 81-96.

Mumford J, 1993. WHO/OIE Meeting: Consultation on newly emerging strains of equine influenza. Vaccine 11: 1172-1175.

Nishiura H and Satou K, 2010. Potential effectiveness of public health interventions during the equine influenza outbreak in racehorse facilities in Japan, 2007. Transboundary and Emerging Diseases 57(3): 162-170.

Paillot R, 2014. A systematic review of recent advances in equine influenza vaccination. Vaccines 2(4): 797-831.

Patterson-Kane JC et al., 2008. The pathology of bronchointerstitial pneumonia in young foals associated with the first outbreak of equine influenza in Australia. Equine Veterinary Journal 40(3): 199-203.

Powell DG et al., 1995. Outbreak of equine influenza among horses in Hong Kong during 1992. The Veterinary Record 136(21): 531-536.

Qi W et al., 2018. Emergence and adaptation of a novel highly pathogenic H7N9 influenza virus in birds and humans from a 2013 human-infecting low-pathogenic ancestor. Journal of Virology 92(2): e00921-17.

Reperant LA et al., 2012. Influenza viruses: from birds to humans. Human vaccines and immunotherapeutics 8(1): 7-16.

Sagripanti JL and Lytle CD, 2007. Inactivation of influenza virus by solar radiation. Photochemistry and Photobiology 83(5): 1278-1282.

Sendor AB et al., 2022. Avian Influenza, Stat Pearls Publishing.

Shao W et al., 2017. Evolution of influenza a virus by mutation and re-assortment. International Journal of Molecular Sciences 18(8): 1650.

Shortridge KF, 1999. Influenza—a continuing detective story. The Lancet 354: 29.

Shtyrya YA et al., 2009. Influenza virus neuraminidase: structure and function. Acta Naturae 1(2): 26-32.

Singh RK et al., 2018. A comprehensive review on equine influenza virus: etiology, epidemiology, pathobiology, advances in developing diagnostics, vaccines, and control strategies. Frontiers in Microbiology 9: 1941.

Sreenivasan CC et al., 2018. Phylogenetic analysis and characterization of a sporadic isolate of equine influenza A H3N8 from an unvaccinated horse in 2015. Viruses 10(1): 31.

Su S et al., 2015. Epidemiology, evolution, and recent outbreaks of avian influenza virus in China. Journal of Virology 89(17): 8671-8676.

Tamerius J et al., 2011. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environmental Health Perspectives 119(4): 439-445.

Taubenberger JK and Morens DM, 2008. The pathology of influenza virus infections. Annual Review of Pathology 3: 499.

Trombetta CM et al., 2019. Influenza D virus: Serological evidence in the Italian population from 2005 to 2017. Viruses 12(1): 30.

Trombetta VK et al., 2018. Are rapid influenza antigen tests still clinically useful in today's molecular diagnostics world? Hawai'i Journal of Medicine and Public Health 77(9): 226.

Van Dijk JG et al., 2015. Weak negative associations between avian influenza virus infection and movement behaviour in a key host species, the mallard Anas platyrhynchos. Oikos 124(10): 1293-1303.

Van Maanen C and Cullinane A, 2002. Equine influenza virus infections: an update. Veterinary Quarterly 24(2): 79-94.

Vega-Rodriguez W and Ly H, 2023. Epidemiological, serological, and genetic evidence of influenza D virus infection in humans: Is it a justifiable cause for concern?. Virulence 14(1): 2150443.

Vemula SV et al., 2016. Current approaches for diagnosis of influenza virus infections in humans. Viruses 8(4): 96.

Venkatesh D et al., 2018. Avian influenza viruses in wild birds: virus evolution in a multihost ecosystem. Journal of Virology 92(15): e00433-18.

Virmani N et al., 2010. Descriptive epidemiology of equine influenza in India (2008-2009): temporal and spatial trends. Veterinaria Italiana 46: 449-458.

Voorhees IE et al., 2017. Spread of canine influenza A (H3N2) virus, United States. Emerging Infectious Diseases 23(12): 1950.

Wang J et al., 2022. Epidemiology of influenza virus reinfection in Guangxi, China: a retrospective analysis of a nine-year influenza surveillance data: Characteristics of influenza virus reinfection. International Journal of Infectious Diseases 120: 135-141.

Wang Y et al., 2020. Emergence, Evolution and Biological Characteristics of H10N4 and H10N8 Avian Influenza Viruses in Migratory Wild Birds Detected in Eastern China in 2020. Microbiology Spectrum 10(2): e00807-22.

Webster RG, 1993. Are equine 1 influenza viruses still present in horses?. Equine Veterinary Journal 25(6): 537-538.

Willoughby R et al., 1992. The effects of equine rhinovirus, influenza virus and herpesvirus infection on tracheal clearance rate in horses. Canadian Journal of Veterinary Research 56(2): 115.

Wonderlich ER et al., 2017. Widespread virus replication in alveoli drives acute respiratory distress syndrome in aerosolized H5N1 influenza infection of macaques. Journal of Immunology 198: 1616–1626.

Wong SS and Yuen KY, 2006. Avian influenza virus infections in humans. Chest 129(1): 156-168.

Woodland RM, 2013. Influenza vaccine strains: Licensing perspectives. Equine Veterinary Journal 45(6): 772-773.

Wu Q et al., 2022. Influenza A virus modulates ACE2 expression and SARS-CoV-2 infectivity in human cardiomyocytes. Iscience 25(12): 105701.

Yamanaka T et al., 2009. Interspecies transmission of equine influenza virus (H3N8) to dogs by close contact with experimentally infected horses. Veterinary Microbiology 139(3-4): 351-355.

Yamanaka T et al., 2012. No evidence of horizontal infection in horses kept in close contact with dogs experimentally infected with canine influenza A virus (H3N8). Acta Veterinaria Scandinavica 54(1): 1-5.

Yang R et al., 2022. Human infection of avian influenza A H3N8 virus and the viral origins: a descriptive study. The Lancet Microbe 3(11): e824-e834.

Yuen KY et al., 1998. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. The Lancet 351(9101): 467-471.

Zhang L et al., 2022. Clinical features of the first critical case of acute encephalitis caused by the avian influenza A (H5N6) virus. Emerging Microbes and Infections 11(1): 2437-2446.

Zhao G et al., 2012. Novel reassortant highly pathogenic H5N2 avian influenza viruses in poultry in China

23

Impact of Food-Borne Diseases in Association to One Health Concept and Efforts of their Prevention

AUTHORS DETAIL

Jwaria Shakeel[1], Taqveem Khalil[2], Maham Khalil[3,] Nimra Shakeel[4], Rizwan Shukat[5], Muhammad Tahir Aleem[6], Irfan Shaukat[7]*, Aftab Shaukat[8]*, Rida Asrar[9] and Hamza Sharafat[10]

[1]Faculty of Veterinary Science, University of Agriculture Faisalabad, 38000, Pakistan
[2]Faculty of Veterinary Science, University of Agriculture Faisalabad, 38000, Pakistan
[3]Centre of Agricultural Biochemistry and Biotechnology (CABB), University of Agriculture Faisalabad, 38000, Pakistan
[4]Centre of Agricultural Biochemistry and Biotechnology (CABB), University of Agriculture Faisalabad, 38000, Pakistan
[5]Faculty of Food, Nutrition & Home Sciences, University of Agriculture, Faisalabad 38000, Pakistan
[6]MOE Joint International Research Laboratory of Animal Health and Food Safety, College of Veterinary Medicine, Nanjing Agricultural University, Nanjing 210095, Jiangsu, PR China
[7]Department of Biochemistry, University of Narowal, Narowal 51600, Pakistan
[8]Department of Clinical Medicine and Surgery, University of Agriculture Faisalabad, 38000, Pakistan
[9]Institute of Physiology and Pharmachology, Faculty of Veterinary Sciences, University of Agriculture Faisalabad, 38000, Pakistan
[10]Veterinary Research Institute Lahore, Pakistan
*Corresponding author: irfan.shaukat@uon.edu.pk; aftabshaukat40@gmail.com

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INTRODUCTION

According to the recent scenario of food consumption, several acute diseases are generally considered to be transmitted by contaminated food. Toxicants or pathogens are normally involved in the contamination of the food. This contaminated food has the enough levels of toxicants or the pathogens which lead the person towards illness (Bhaskar 2017).

The Food borne diseases have been categorized as: Food borne intoxications, Foodborne toxico infections and Food borne infections (Fig. 1) (DeWaal et al. 2006).

Food borne infections are caused by the interaction of the microorganisms' toxic to the body and ingested by the person through contaminated food where these pathogenic microorganisms react with the other body tissues and trigger the disease. These microorganisms may be parasitic, viral, bacterial, or fungal (Gallo et al. 2020). The food borne infections caused by bacteria include Cholera, typhoid fever, salmonellosis, shigellosis, Campylobacteriosis, Yersiniosis, *Escherichia coli* infection, Listeriosis and Vibrio parahemolyticus. Viral food borne infections include poliomyelitis virus, hepatitis A and Norwak virus. Fungal food borne infections include Sporothrix spp., Wangiella spp., Candida spp., etc. (Akhtar et al. 2014).

The consumption of food containing poisonous compounds, metabolic toxins (made and omitted by microorganisms such as algae, fungi and bacteria) and bio toxicants (formed in certain tissue of animals and plants) are the main factors of foodborne intoxications. These Food borne intoxications have been classified as:

a. Fungal intoxications b. Bacterial intoxications c. Poisonous animals d. Chemical intoxication e. Plant toxicants (Sudershan et al. 2014).

Foodborne toxicoinfections are mainly caused by toxico-infectious agents like enterohemorrhagic *Clostridium perfringens* and *Escherichia coli* (Nazem et al. 2016).

The main symptoms of foodborne diseases are based upon the source of food. The most commonly observed symptoms are abdominal pain, vomiting, bloody or simple diarrhea, chills, fever and other pathogen-specific signs. The disease can lead from acute to chronic cases depending upon the range of symptoms which can last from few days to months. There are some bacteria like *C. botulinum* with some chemical substances result in alarming situation by damaging the nervous system with the symptoms of paralysis, blurred vision, dizziness, headache, weakness, and numbness or tingling of the skin (Fein et al. 1995).

To manage the turn up of zoonoses, One Health's focus is preferably considered on the convergence of environment, animal and human health. The food-borne infection entails different pathways thus these criteria of convergence are undefined and complex (Lake and Barker 2018). The food production from animal sources is thought to be the main cause of spread of food-borne infections. The food products from animals such as meat, milk etc. may have the

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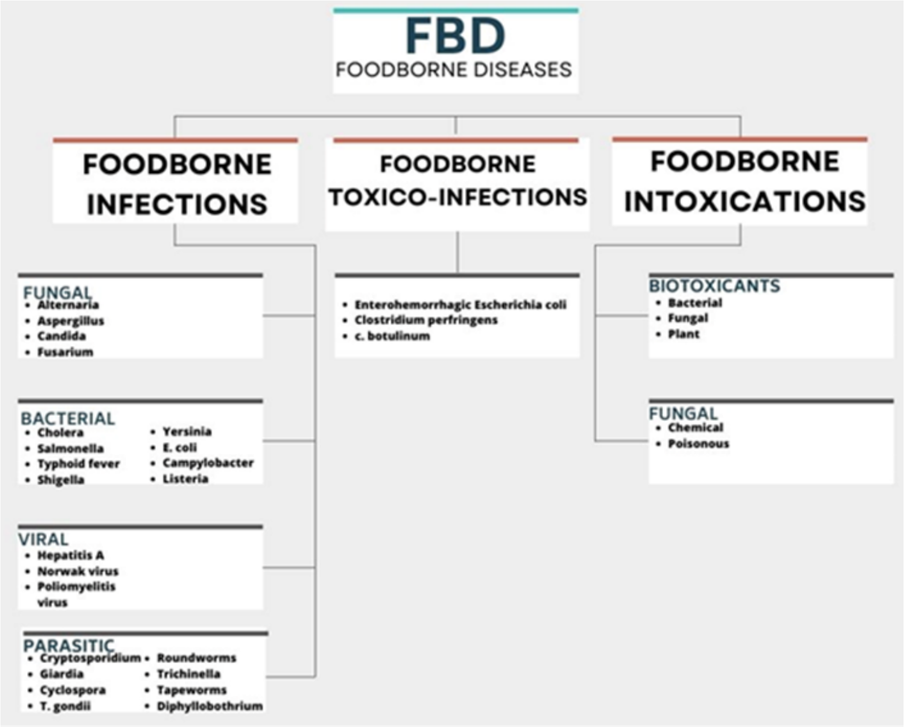

Fig. 1: Classification of Food Borne Diseases

highest rate of contaminants, pathogen contents, adulterants and natural toxins. It has been observed that with the high consumption of food products derived from animals, the rate of food-borne diseases is amplifying day by day leading to increase in death rate (Barber et al. 2003).

The contamination of food products may occur on any division of the food chain or may be at food production level where different processes are taking place in different food units to make purified food products. The toxification of the food depends on the hygienic condition of the place for food production and the health condition of workers. With proper knowledge and practice to keep up the hygienic condition, the risk of food contamination can be reduced to a minimum level (Mudey et al. 2010).

In the past few years, the food-borne pathogenic microorganisms have become the main concern due to their severe effect on health worldwide. These are not only affecting health but also putting impact on the economy at a huge level. According to different surveys, it has been concluded that more than half of human diseases are derived from animals and some chronic diseases are being spread by vertebrates to human. Approximately 500 million people in the world are suffering from food-borne diseases by consuming contaminated food each year (Newell et al. 2010). For the detection of the common food-contaminating bacteria and their toxin production rate in food different methods such as molecular techniques, conventional (culturing) and serological methods are being implied by the researchers. To control and prevent these diseases, the most effective methods for food purifications are pasteurization procedures, execution of standard HACCP protocols, a good hygienic environment, and sanitation in operating procedures (Newell et al. 2010). These foodborne diseases are directly linked to countries where the poverty level is high but is putting an impact on the health of the people on a global scale (Grace 2015). With the increase in trade between international markets and the complexity of the food chains, the rate of contamination of food is at its peak because infected food products are being transported across the countries. Climate change, growing cities, growing international travel, and migrations are the main causes that introduce people to endangerment (Bhaskar 2017).

Social Impact of Food-borne Illnesses

The major source of increase in morbidity rate in most of the developed countries is found to be foodborne ailment. In United States, there are almost 48.7 million recorded cases in a year due to food contamination. This estimation of the disease includes 30 main foodborne disease-causing pathogens, and the remaining are the cases in which the source in unidentifiable (Newman et al. 2015). There are about 245 infectious and not infectious pathogens that produce toxins to contaminate food on production level leading towards the hazardous state (Todd 1989). By keeping in view all the complexities related to foodborne diseases, the contamination of the food can occur at any stage from its production level to food consumption. With the utilization of this contaminated food, 430,000 deaths have been recorded each year as one in 10 people is suffering from a foodborne disease (Newman et al. 2015). Mostly children under the age of 5 year get caught by the disease and their mortality rate has reached 120, 000 per year. Diarrheal diseases have been examined in most cases. Some other serious outcomes of these foodborne diseases comprise neural and brain disorders, liver and kidney failure, cancer, and reactive arthritis which all lead toward death (Yenealem et al. 2020).

Economic Impact

According to the recent findings of World Bank it is concluded that the low and middle class suffer more due to the infectious food which also put a huge impact on the economy of country. Due to the medical expenses and low productivity, there is a loss of US$ 120 billion each year. However, these expenses can be overcome by introducing proper hygienic environment during food production and proper assessment should be carried out to improvise the transportation of food without contamination. Proper protocols should be developed under the Act of food security to achieve the goals for better management of food production which will be helpful to vanquish the major problems like hunger and poverty (Attina and Trasande 2013).

According to the survey of WHO (World Health Organization), the Foodborne affliction caused 440,000 deaths and 700 million got affected by consuming infectious food in 2010. This trial of foodborne diseases caused a devastating impact worldwide. In comparison, non-developed and underdeveloped countries like Southeast Asia, sub-Saharan Africa, and South Asia suffered relatively more due to this outbreak (Havelaar et al. 2015). Based on global population, 55 percent of people are suffering from foodborne diseases and 75 percent of deaths have been recorded so far. This whole situation of diseases and deaths is alarming for young children's health if they consume unhealthy food. Almost 10 percent of the world's population consists of children under the age of 5 years. But due to food borne diseases, there are 50 percent of illnesses and 40 percent of deaths have been recorded in children (Yenealam et al. 2020). The yearly cost of the medication is estimated to be US$ 20 billion and the total loss of US$ 94.5 billion have been recorded due to less production effected by the food borne diseases in non-developed countries each year. Many other losses such as foregone trade market, losses of companies and farms, the health sector which are practicing their best to provide high-nutrient food, and most important the burden on the environment due to the wastage of food are non-quantifiable (Hoffmann et al. 2012).

Food Borne Diseases _ A Major Health Problem for Developing Countries

The major problems related to health are the Food-borne diseases both in developing and developed states, but it has been observed that the developing countries undergo more devastation due to these diseases as compared to developed countries (Todd 1989). In developed countries, 40% of the population gets afflicted by foodborne diseases with an estimated 3 million mortalities according to recent studies by WHO (Havelaar et al. 2015).

Expeditious geographical changes and dietary modifications are playing vital role in exposing folks to foodborne infections in underdeveloped countries. Food safety management is required to prevail a proper healthy environment (Scharff 2012). Health care systems, human health, and livelihood are greatly affected by these diseases across the world. However, developing countries have got restricted by these diseases to trade their products globally for the betterment of their economy (Todd 1989).

Due to the pollutants and pathogens, most of the food get contaminated leading towards the foodborne diseases which has been examined in almost 500 million people across the globe. Unfortunately, most of the world's population reside in the developing countries where proper medications and equipment are absent to cure the diseases. The developing countries also don't have good economies and health care systems to stabilize themselves from these foodborne diseases (Hoelzer et al. 2018).

For the survival in developing countries, the world needs to get united to overcome the destruction caused by these diseases. There is a need to aware the people about the pathogens transmitted from animal source through food products and their impacts on the health with the protocols of food security to save the economy and mankind. With the trade of new food products, there is a chance of exposure of new pathogens and their pathways which will be more challenging to overcome unless proper preventive measures will not be taken (Starbird 2000). Due to animal farming and the use of drugs for the treatment of humans, the foodborne pathogens are getting resistant whenever contaminant food is consumed. These resistant or susceptible bacteria are leading to more serious diseases. Foodborne pathogens are the main cause of concern nowadays and drug resistant pathogens are becoming more lethal (Xu et al. 2020).

The common reasons for the emergence of foodborne disease in the developing countries i.e., Ethiopia, are the lack of education for handling of food, poor sanitation practices, improper food safety protocols, low investments, lack of resources for food production and absence of regulatory systems. To prevent diseases from spreading, different awareness session has been conducted to ponder over the impact of foodborne pathogens on health (Tassew et al. 2010). However, it is necessary to develop proper documentation, rules, and food safety laws on the emergence of these diseases. Due to the poor reporting systems in most developing countries like Ethiopia, these diseases are overcoming the population rapidly (Ayana et al. 2015).

One Health Concept and Food Safety

To commence the concept of the 'One Health' approach, a simple explanation is enough that it's the combination of efforts by various disciplines working on a local, national, and global platform to accomplish favorable well-being of people and animals in a healthy environment (Abebe et al. 2020). One Health is addressing many convoluted issues with the health of livings by representing an expeditious range in the growth of cooperating disciplines which includes ecosystem health, food security, communal and animal health, health economics, social science, and ecosystem health. There is a direct relationship between the robustness of the living and the planet based on the daily production and consumption of food (Chakraborty and Newton 2011).

With the passage of time, since the last century, the distance of 'farm to fork' has reduced on the global level which means that the ingredients required for the preparation of a single meal are available at a global scale along with a local source. The consignment of common or whole ingredients to the table from the farm has become possible by one health food safety approach without traveling throughout the world. The surety of the safest food supply in the world mainly depends upon the well-being of humans and animals and the health of crops (Marilena 2012).

Food-borne infections are more likely to arise, reappear, and spread because of the expansion of food production, which also makes it more difficult to predict, identify, and successfully address these hazards to public health. Each year, food-borne infections result in over 48M infections, 128,000 get hospitalized, and 3,000 fatalities in the United States alone. Foodborne infections can also be non-zoonotic in nature, but there are several foodborne zoonoses of public health significance in Europe (Koutsoumanis et al. 2018). They all share the need for a One Health approach to manage food safety and comprehend the factors that influence the onset and persistence of risks to people, animals, and the climate (Osterhaus et al. 2020).

Involvement of Various Food Resources in Food-Borne Illness

Source imputation, also known as a pathogen account, is a crucial tool for estimating the contribution of different food resources to foodborne illness, enable management and intervention methods for safe food and the health of people. Knowing the portion that can be attributed to elements other than food, such as exposure to the environment, direct contact with animals, and human-to-human interaction, is crucial for developing food safety policies (Galimberti et al. 2020).

The main causes or reservoirs of human foodborne illness can alter over time. For instance, laying hens' *Salmonella* levels significantly decreased with the establishment of EU-wide control regulation for the pathogen (Koutsoumanis et al. 2019). The risk of salmonellosis among Swedish visitors to the EU has decreased by around 50% because of this control regulation, and the number of salmonellosis cases that have been documented in humans has decreased significantly. All EU countries have reached the same degree of control as Sweden and as by Finland, which began implementing prevention strategies against *Salmonella* in animals used for food production in the 1960s (Koutsoumanis et al. 2019).

According to reports, foodborne infections of animal origin are responsible for around two-thirds of these infections burden of the Netherlands, with human-to-human spread coming in second and environmental dissemination coming in third. Similar findings were made by Adak and his team, who discovered that foodborne illness was to blame for between 63-99% of STEC O157, *Campylobacter* spp., *L. monocytogenes*, and non-typhoidal *Salmonella* cases. The main cause of comparatively large burden of environmental dissemination was *Toxoplasma (T.) gondii* (Shapiro et al. 2019).

Combinations of Pathogens and Food Commodities: One Health Issues

From 1998 to 2013, there were more norovirus notifications in the EU. Despite not being a zoonotic agent, norovirus nevertheless has a significant impact on one health due to its ability to spread through food, water, and person-to-person contact (Osterhaus et al. 2020). Fig. 2 illustrate the timeline of various foodborne outbreaks due to different pathogens.

According to reports, vegetables and cereals, seasonings, fruits, sprouts and botanicals have been the leading sources of contamination for norovirus eruption in the EU. The raspberries which have been passed through heat treatment are one of those goods that frequently cause infections, for example, in countries like Sweden, Norway, Denmark, France and Finland. One factor contributing to this is the rising popularity of eating wholesome, lightly refined carbohydrates, such as goods like smoothies and paneer made with fruits or cherries (Meghwal and Goyal 2018).

Before eating, raspberries either go through minimal preparation or no processing at all, hence there is no pathogen deactivation procedure (Butot et al. 2018). This has made it easier to distribute raspberries that might be norovirus-contaminated, along with market liberalization. The number of berries consumed in the EU increased by 4.5 times from 1988-2005. Additionally, imports of smooth frozen fruits into Europe for manufacturing increased by a factor of 2.5 between the late 1980s and the early 2000s (Osterhaus et al. 2020).

It is challenging to lower the danger of contracting norovirus by eating berries due to the extended living time of norovirus and a modest reduction in infection rates while storage. 90% or > 1log of the virus is rendered inviable by freezing, which is insufficient to totally eradicate the danger of infection (Meghwal and Goyal 2018). As an illustration, research on outbreaks has revealed that raspberries that have been preserved for days or weeks can serve as a source of norovirus infection. Processing procedures include mixing samples from wide varieties before freezing and packaging frozen berries can result in widespread cross contamination which can ultimately lead to disease outbreaks. Tracking the outbreaks and tracing compromised raspberry batches has

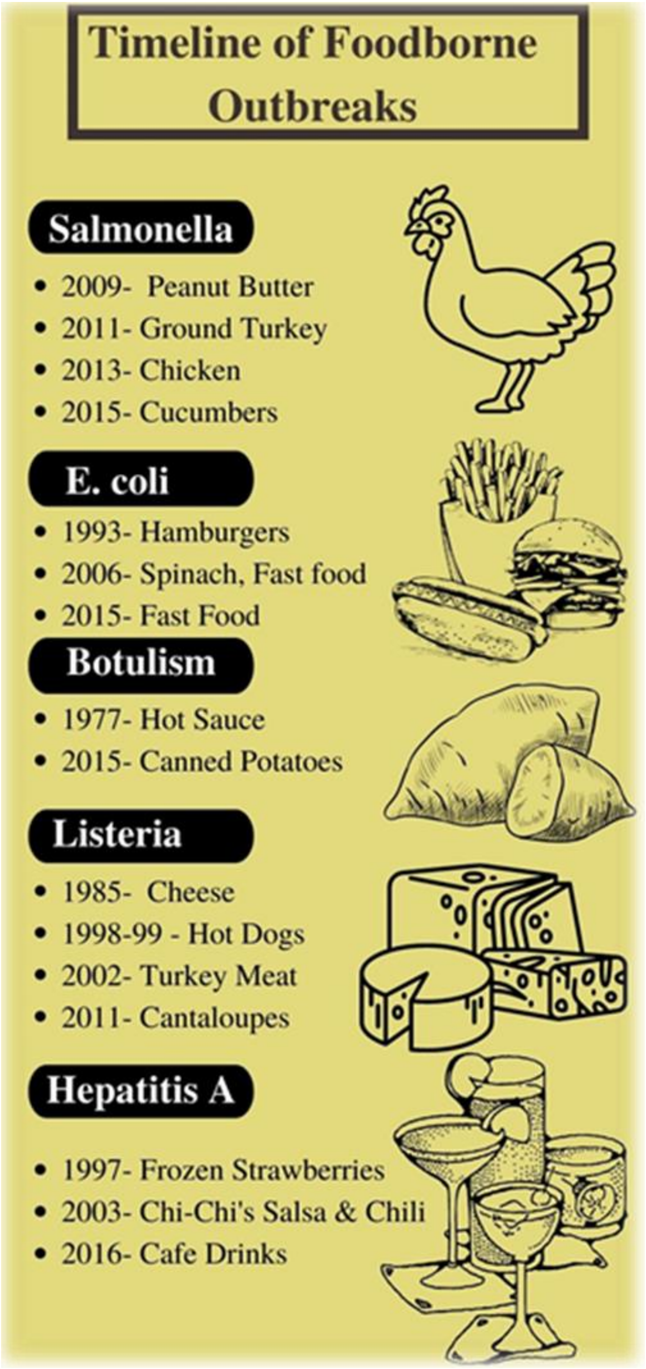

Fig. 2: Timeline of Foodborne outbreaks

revealed intricate distribution networks. A bunch of frozen raspberries can come from over 60 distinct farms, many of which are small-scale farmers. Due to this, it is challenging to identify the farms where the agent was first introduced (Butot et al. 2018).

The most favorable time for the virus infection to occur is during production, explicitly throughout the irrigation with tainted water or during compendium by food attendants' hands, especially if there are inadequate hygiene conditions present during harvest, such as a scarcity of toilets and amenities to wash hands (Butot et al. 2018). An evaluation of the exposure to human norovirus along with a farm-fork hazard identification model has established the significance of norovirus contamination through hand touch (Osterhaus et al. 2020). The correlation between the occurrence of norovirus and colonic discharge markers like *E. coli* highlights the danger of sewerage and drainage infiltration of irrigation waterways (Koutsoumanis et al. 2019).

Shiga Toxin-Producing *Escherichia Coli* (STEC) in Sprouts

The fourth most typical zoonotic disease in the EU is STEC infection (Libera et al. 2022). Beef is thought to be a significant source of human foodborne STEC infections, and cattle are the primary recognized STEC reservoirs. A distinct *E. coli* strain (STEC O104:H4) that wasn't considered as a public health significance was discovered in Northern Germany in 2011. More than 3,800 people became ill because of this pandemic, which also affected many EU nations and resulted in more than 50 fatalities (Libera et al. 2022). An outbreak of Shiga toxin-resistant *E. coli* (STEC) was brought on by a microbe that gained the capacity to manufacture Shiga toxin through horizontal gene transfer. There may be a human reservoir for the strain as people and animals had not been frequently described as carriers (Lee et al. 2021).

Ripened seeds have been classified as STEC and *Salmonella* high-risk foods. In 1996, Japan saw the greatest outbreak related to sprouting seeds (Koutsoumanis et al. 2019). The primary cause of outbreaks in these items is bacterial contamination of dry seeds (Machado-Moreira et al. 2019).

During sprouting, the high humidity and favorable temperature might result in pathogen infection. *Salmonella* and STEC O157:H7 vaccines have been found to successfully disinfect using hot water treatment. *Listeria monocytogenes* and *Salmonella* food safety standards were established in EU Regulation (EC) No. 2073/2005, which was later updated to include an *E. coli* process hygiene standard (Var et al. 2021).

Listeria monocytogenes' Significance in Packaged Foods

Human listeriosis has been on the rise since 2008, and in 2015 it was the fifth-most often reported zoonotic disease in the EU (Libera et al. 2022). *Listeria (L.) monocytogenes* is so common in nature that it may infect a broad variety of foods (Var et al. 2021). Most outbreaks that have been recorded inside the EU have included prepared, chilled foods of animal origin that have been processed, such as soft cheeses, smoked salmon, and delicatessen meats (Machado-Moreira et al. 2019). Meals of a plant-based origin, such as melon and toffee apples, or even frozen foods, have been linked to the outbreaks across the world (Starbird 2000).

A wide variety of pH values, high salt concentrations, and refrigeration temperatures are favorable for *L. monocytogenes* growth (Var et al. 2021). The heat methods employed in the manufacturing of some RTE (ready-to-eat) meals inactivate the bacteria. Food enterprises are advised to check processing facilities and equipment for the presence of *L. monocytogenes* in accordance with EU food hygiene laws (Libera et al. 2022).

Antimicrobial Resistance as a Foodborne One Health Problem

One Health concerns about the foodborne consumer exposure to bacteria with genes coding for resistance to specific antibiotics (Xu et al. 2022). According to surveillance of broilers in Swedish slaughterhouses, between 25 and 50 percent of broiler carcasses were contaminated with Enterobacteriaceae that produce extended-spectrum beta-lactamases (Ibrahim et al. 2022).

In a setting devoid of antimicrobials, resistant bacteria will initially less viable and less able to proliferate than sensitive germs (Konai et al. 2018). Antibiotic usage is linked to greater mutation rates, which increases the possibility of resistance development. The fitness costs of resistance may also be decreased by these modifications. If present in consumables, bacteria that have genes for antimicrobial resistance (AMR) can spread very quickly (Ibrahim et al. 2022). AMR genes can survive in commensals, such as bacteria, or on pathogens (Xu et al. 2022). They can also move between various bacterial species as they move up the food chain. Foods are effective means of spreading AMR germs to consumer and expose them to those bacteria (Konai et al. 2018).

Systems for producing food must be created to stop the transfer of resistant microorganisms to consumer. For instance, it appears that a significant source of quinolone-resistant *Campylobacter spp.* is chicken meat (Schweitzer 2022). Poultry, pig, and beef are suspected dietary sources of cephalosporin resistance. Any further bacterial resistance among food-borne germs is likely to increase human exposure and the threats to the general public's health (Ibrahim et al. 2022).

Antimicrobial usage in food animals has significant side effects because it fosters the growth and survival of AMR zoonotic bacteria (Konai et al. 2018). AMR is typically listed as one of the main issues in One Health conversations where veterinary and public health sectors need to work together. Aarestrup and Wegner underlined the urgent need to put methods for reducing and managing AMR into place about 20 years ago (Xu et al. 2020).

Bovine Spongiform Encephalopathy and One Health Challenges

"Mad cow disease" or "bovine spongiform encephalopathy" refers to illnesses that damage the brain and nervous system in both humans and animals (Schweitzer 2022). The zoonotic illness BSE, which affects cattle, results in variant Creutzfeldt-Jakob disease (vCJD) in humans. In rendering process in UK in the late 1970s, an established cycle of nutrients was altered (feeding ruminant-derived meat-and-bone meal to cattle and calves), which allowed the BSE agent to circulate and grow. To boost yields and lower costs for dairy production, a novel feeding method based on nutrient recycling has been created (Mudey et al. 2010). The rendering procedure included enough heat treatment to guarantee the eradication of zoonotic and animal diseases including *Salmonella* and the CSF virus (Schweitzer 2022).

A Brief History

- The first episodes of BSE in cattle were discovered in UK in December 1984, and the disease wasn't formally recognized until two years later (Ibrahim et al. 2022).
- De Koeijer concluded that through the cycle of cow feed, MBM and rendering, one sick cow could often infect 15 to 20 more cows. Later, it was discovered that the prion protein formed in the brains of vCJD patients was identical to that of BSE-affected cattle (Abelman 2020).
- Like vCJD patients, BSE-inoculated macaques also had neuropathological alterations. Later, studies proved that BSE is a zoonotic issue (Abelman 2020).
- The initial BSE control measures were implemented in the United Kingdom in 1984, with the first clinical symptoms occurring in 1989/90. Because they saw BSE as a UK issue during the 1980s and 1990s, other European nations did not take comparable steps (Kamali-Jamil et al. 2021).
- The presumption of disease freedom in an area or nation is based on the lack of exposures or risk factors throughout the illness's incubation phase. Due to their rendering and feeding practices, nations that bought MBM from the UK cattle were at a high risk of spreading the BSE pathogen (Var et al. 2021).

Preventive Measures

The majority of food-borne diseases are avoidable. When developing control techniques for foodborne diseases, technical information on pathogen transmission channels is essential.

A **One Health strategy** is required to decrease food waste and maximize nutrient utilization by adopting closed circular food systems. However, for these methods to be effective, consumer behavior, food trends, economic incentives, trade, and politics must all be considered (Koutsoumanis et al. 2019). Because of this, effective One Health programs are built on an awareness of the socioeconomic settings of farmers, food industry professionals, and consumers (Osterhaus et al. 2020).

Innovations in refrigeration, transportation (by air, sea, and land) and instant communication enable food distribution systems to deliver perishable foods quickly, offer just-in-time resupply of non-perishable foodstuffs, and benefit from economies of scale (Koutsoumanis et al. 2019).

Control measures for major reservoirs will minimize continued host exposure, regardless of the route of transmission and carrier (Yenealem et al. 2020). For example: During the BSE crisis of 1996, the European Union enacted harsh restrictions to stop the disease's spread including a complete prohibition on animal MBM in animal feed across the EU and the testing of all animals older than 30 months for prions at the time of slaughter (Kamali-Jamil et al. 2021; Galimberti et al. 2022).

The goal of operators during production should be based on good manufacturing practices (GMP), good hygiene practices (GHP), and good agriculture practices (GAP) (Butot et al. 2018).

A risk-based approach to combat foodborne diseases should be utilized, instead of a hazard-based approach, from a public health standpoint. One example of a hazard-based strategy is the focus on controlling *Salmonella* in commodities. This has largely been successful, but it has not necessarily improved the food safety situation, due to *Campylobacter spp.* foodborne zoonosis (Libera et al. 2022). The example indicate that management in primary manufacturing and secondary processing is vital for decreasing pathogens' incidence in the food web. An increase in consumption of raw or little processed food offers significant hurdles for products that needs a high level of physical handling (Butot et al. 2018).

Avoid the emergence and subsequent spread of resistant bacteria or resistance genes to deal with the situation of antimicrobial resistance (AMR) (Xu et al. 2020). Therefore, the widespread use of antimicrobial agents in veterinary medicine to treat food and companion animals is not sustainable anymore (Safi et al. 2018).

Use of Preventative medicine must be encouraged, such as:

- Better biosecurity, fortification of animal health and welfare within production systems
- Ease in vaccination to protect against infections
- More animal breeding programs aimed at breeding animals having strength and resilience (Kumagai et al. 2019)

Food security, nutrition, and disease control must all be prioritized at the same time since they are not mutually exclusive goals. The food chain has a high level of diversity. Without tight One Health collaboration amongst all stakeholders, finding the appropriate answers to today's problems would be challenging (Hoelzer et al. 2018).

Conclusion

Globally, foodborne disease spread and acquisition has a direct link with One Health triad due to its involvement in public health and hygiene issues. Factors involving in the spread of these infections include the improper handling of food from production till consumption. According to the survey, E. coli, Salmonella and Campylobacter are the leading infectious causes. The continued globalization of the food supply, the effects of international travel and tourism, and the effects of foodborne illness on poor countries are some domestic food safety challenges for the twenty-first century. Several nations have started nationwide programs to limit the frequency of foodborne illnesses, including informing people about the importance of practicing food safety. Consumer hygiene products and hygiene practices are being improved and geared towards high-risk areas, such as limiting the spread of foodborne illness to other people through inanimate objects. Using new techniques to recognize, track, and evaluate foodborne dangers will be necessary to meet the enormous issue of food safety in the twenty-first century. The use of both established and emerging technologies to ensure food safety should be enhanced which strives for "health for all".

REFERENCES

Abebe E et al., 2020. Review on major food-borne zoonotic bacterial pathogens. Journal of Tropical Medicine.

Abelman H, 2020. Cripping mad cow disease. Jenkins S and Montford KS, editors. Disability and Animality: Crip Perspectives in Critical Animal Studies; pp: 212-220.

Akhtar S et al., 2014. Microbiological food safety: a dilemma of developing societies. Critical Reviews in Microbiology 40: 348-359.

Attina TM and Trasande L, 2013. Economic costs of childhood lead exposure in low-and middle-income countries. Environmental Health Perspectives 121(9): 1097-1102.

Ayana Z et al., 2015. Food-borne bacterial diseases in Ethiopia. Journal of the Academy of Nutrition and Dietetics 4: 62-76.

Barber DA et al., 2003. Models of antimicrobial resistance and foodborne illness: examining assumptions and practical applications. Journal of Food Protection 66(4): 700-709.

Bhaskar SV, 2017. Foodborne diseases—disease burden. Food safety in the 21st century, Academic Press, Cambridge, Massachusetts, USA.

Butot S et al., 2018. UV-C inactivation of foodborne bacterial and viral pathogens and surrogates on fresh and frozen berries. International Journal of Food Microbiology 275: 8-16.

Chakraborty S and Newton AC, 2011. Climate change, plant diseases and food security: an overview. Plant Pathology 60: 2-14.

DeWaal CS et al., 2006. Foods associated with foodborne illness outbreaks from 1990 through 2003. Food Protection Trends 26: 466-473.

Fein SB et al., 1995. Foodborne illness: perceptions, experience, and preventive behaviors in the United States. Journal of Food Protection 58(12): 1405-1411.

Galimberti A et al., 2020. Rethinking urban and food policies to improve citizens safety after COVID-19 pandemic. Frontiers in Nutrition 7: 569542.

Gallo M et al., 2020. Relationships between food and diseases: what to know to ensure food safety. Food Research International 137: 109414.

Grace D, 2015. Food safety in low- and middle-income countries. International Journal of Environmental Research and Public Health 12(9): 10490-10507.

Havelaar AH et al., 2015. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. PLoS Medicine 12(12): e1001923.

Hoelzer K et al., 2018. Emerging needs and opportunities in foodborne disease detection and prevention: From tools to people. Food Microbiology 75: 65-71.

Hoffmann S et al., 2012. Annual cost of illness and quality-adjusted life year losses in the United States due to 14 foodborne pathogens. Journal of Food Protection 75(7): 1292-1302.

Ibrahim T et al., 2022. Detection of extended spectrum beta-lactamase (ESBL)–production in Salmonella typhimurium isolated from poultry birds in Nasarawa State, Nigeria. Scientific African 16: e01243.

Kamali-Jamil R et al., 2021. The ultrastructure of infectious L-type bovine spongiform encephalopathy prions constrains molecular models. PLoS Pathogens 17: e1009628.

Konai MM et al., 2018. Recent progress in polymer research to tackle infections and antimicrobial resistance. Biomacromolecules 19: 1888-1917.

Koutsoumanis K et al., 2018. Public health risks associated with food-borne parasites. EFSA Journal 16: e05495.

Koutsoumanis K et al., 2019. Salmonella control in poultry flocks and its public health impact. EFSA Journal 17: e05596.

Kumagai S et al., 2019. Bovine spongiform encephalopathy–a review from the perspective of food safety. Food Safety.

Lake IR and Barker GC, 2018. Climate change, foodborne pathogens and illness in higher-income countries. Current Environmental Health Reports 5(1): 187-196.

Lee IPA et al., 2021. Bacterial cooperation through horizontal gene transfer. Trends in Ecology and Evolution.

Libera K et al., 2022. Selected livestock-associated zoonoses as a growing challenge for public health. Infectious Disease Reports 14: 63-81.

Machado-Moreira B et al., 2019. Microbial contamination of fresh produce: What, where, and how? Comprehensive Reviews in Food Science and Food Safety 18: 1727-1750.

Marilena NO, 2012. Agricultural Market Stability in the Future Common Agricultural Policy. Mediterranean Journal of Social Sciences 3: 251-251.

Meghwal M and Goyal MR 2018. State-of-the-art technologies in food science: human health, emerging issues and specialty topics, CRC Press, Florida, USA.

Mudey AB et al., 2010. Health status and personal hygiene among food handlers working at food establishment around a rural teaching hospital in Wardha District of Maharashtra, India. Global Journal of Health Science 2(2): 198.

Nazem AM et al., 2016. Toxic-infectious Bacteria in Raw Milk and Soft Cheese in Local Markets. Alexandria Journal for Veterinary Sciences 48(2).

Newell DG et al., 2010. Food-borne diseases—the challenges of 20 years ago still persist while new ones continue to emerge. International Journal of Food Microbiology 139: 3-15.

Newman KL et al., 2015. The impact of socioeconomic status on foodborne illness in high-income countries: a systematic review. Epidemiology and Infection 143(12): 2473-2485.

Osterhaus AD et al., 2020. Make science evolve into a One Health approach to improve health and security: a white paper. One Health Outlook 2(1): 1-32.

Safi S et al., 2018. Acceptance and resistance of new digital technologies in medicine: qualitative study. JMIR Research Protocols 7: e11072.

Scharff RL, 2012. Economic burden from health losses due to foodborne illness in the United States. Journal of Food Protection 75: 123-131.

Schweitzer P 2022. Demographic, Husbandry, and Biosecurity Factors Associated with the Presence of Campylobacter spp. and Tetracycline-and Quinolone-Resistant Campylobacter spp. in Small Poultry Flocks in Ontario, Canada. PhD dissertation, University of Guelph.

Shapiro K et al., 2019. Environmental transmission of Toxoplasma gondii: Oocysts in water, soil and food. Food and Waterborne Parasitology 15: e00049.

Starbird SA, 2000. Designing food safety regulations: The effect of inspection policy and penalties for noncompliance on food processor behavior. Journal of Agricultural and Resource Economics 2000: 616-635.

Sudershan RV et al., 2014. Foodborne infections and intoxications in Hyderabad India. Epidemiology Research International.

Tassew H et al., 2010. Microbial flora and food borne pathogens on minced meat and their susceptibility to antimicrobial agents. Ethiopian Journal of Health Sciences 20(3).

Todd EC, 1989. Costs of acute bacterial foodborne disease in Canada and the United States. International Journal of Food Microbiology 9(4): 313-326.

Todd EC, 1989. Preliminary estimates of costs of foodborne disease in Canada and costs to reduce salmonellosis. Journal of Food Protection 52(8): 586-594.

Var I et al., 2021. Evaluation of Food Safety of Commercial Baby Foods according to Legal Regulations. European Journal of Agriculture and Food Sciences 3: 72-80.

Xu Z et al., 2020. Prevalence and antimicrobial resistance of retail-meat-borne Salmonella in southern China during the years 2009–2016: The diversity of contamination and the resistance evolution of multidrug-resistant isolates. International Journal of Food Microbiology 333: 108790.

Yenealem DG et al., 2020. Food safety practice and associated factors among meat handlers in Gondar town: a cross-sectional study. Journal of Environmental and Public Health.

24

Bacteriophage Therapy: Effective Antibiotic Replacer Against Emerging Ghost of Antimicrobial Resistant Bacteria

AUTHORS DETAIL

Tariq Jamil[1]*, Ayesha Mehmood[1], Muhammad Haris Raza Farhan[6], Fakiha Kalim[2], Fazle Hadi[5], Khadija Younas[3], Qamar Iqbal[5], Rida Asrar[4] and Ahmad Nawaz[5]

[1]Institute of Microbiology, Faculty of Veterinary Science, University of Agriculture Faisalabad, Pakistan
[2]Department of Parasitology, University of Agriculture, Faisalabad, Pakistan
[3]Department of Theriogenology, Faculty of Veterinary Sciences, University of Agriculture, Faisalabad 38040
[4]Faculty of Veterinary Science, University of Agriculture Faisalabad- 38040, Pakistan
[5]Faculty of Veterinary Sciences, University of Agriculture, Faisalabad, Pakistan-38000
*Corresponding author: tariq.jamil154@gmail.com

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INTRODUCTION

The battle with infectious diseases is always a burning issue. Up to the early 1900s, infectious diseases were the Primary cause of mortality e.g. the mortality rate in England was 25% due to infectious diseases. But, after the marketing of antibiotics, this mortality rate declined to less than 1% (Watkins and Bonomo 2012) The commercialization of antibiotics is considered an important achievement in the field of medicine. Selman Waksman was the first to describe the term ‘antibiotic’ as any small molecule produced by microbes that acts against the growth of other microbes (Clardy and Fischbach 2009). Antibiotics act either cytostatically or cytotoxically against the micro-organisms and thus, help the body’s immune system to eradicate them. Mainly, antibiotics act by inhibiting protein synthesis, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and bacterial cell synthesis(Levy and Marshall 2004). The war against infectious diseases was considered won due to the discovery of antibiotics. But, the tables have turned as many bacteria have become resistant to these antibiotics. Presently, infectious diseases are a remarkable cause of global morbidity and mortality. According to the assessment report WHO, the important causes of morbidity and mortality include diarrheal diseases, HIV/AIDS, lower respiratory infection and malaria (WHO 2014). Fleming was the first to warn that Penicillin can be potentially resistant if used in scarce amounts or for a too short period of treatment (Aminov 2010). Antibiotic resistance occurs when a drug becomes ineffective against the inhibition of bacterial growth. So, the bacteria become resistant and tend to multiply even at therapeutic levels of antibiotics (Bush 2011). Antibiotic resistance can be a natural selection process where all bacteria naturally show a small degree of resistance (Levy 1992). Bacteriophages against the bacterial infection were common in practice before the legal discovery of penicillin. Bacteriophages (shortly called “Phages”) are bacteria-specific viruses that have been used in therapy against pathogens such as *Shigella dysenteriae* as early as 1919 (Chanishvili 2012). Phage therapy against infections has been used for almost a century but recently got more recognition due to the emergence of multi-drug resistant pathogens. Frederick Twort was the first person who explained the lysis related to the phage infection but later the source of this process and the term “Bacteriophage” was firstly described by Felix d’Herelle. Also, the therapeutic use and recorded treatment of phages was done by Felix d’Herelle in 1919 at the Hôpital des Enfants-Malades of Paris. During this struggle, he was able to treat four children from bacterial dysentery successfully (Chanishvili 2012). The early experiments carried out by d’Herelle were known to be poorly controlled despite several successful attempts (Wittebole et al. 2014). However, d’Herelle pursued to development of phage therapy by treating diseases like cholera, bubonic plague, and dysentery in the early 20th century. Many phage therapy centers and commercial phage production units were also developed in Europe and India (Sulakvelidze and Alavidze 2001). Many business persons together with d’Herelle tried to disseminate phage production in the USA and Brazil with various phage preparations for *Streptococcus*, *Staphylococcus*, *E. coli* and other pathogenic (Sulakvelidze and Alavidze 2001). These various preparations were transported to the practitioners. But, as the results of the treatment were not 100% successful so, this situation led to the inclination toward the use of antibiotics in western countries (Chanishvili 2012). In the 1940’s, phage therapy was set aside extensively due to the development of new pharmaceutical antibiotics in the West. The deviation from this situation occurred in the former Soviet Union and Eastern Europe where the treatment involving phage therapy against antibiotic- resistant infections was carried out on a large scale (Weber - Dąbrowska et al. 2001). Antibiotic resistance was

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described as “the greatest and most urgent global risk” by the United Nations General Assembly on September 21, 2016. This review highlights on the applications of bacteriophage therapy against multi-drug resistant bacteria.

Anti-Microbial Resistance

After the discovery of antimicrobial drugs, it was the perception of healthcare community that they had won the battle against microbes. However, many bacteria have become resistant to antibiotics and the battle is seemingly in favor of bacteria. Initially, resistance was observed after the first antibiotic penicillin was introduced to the market in 1941, and just a year later in 1942 penicillin-resistant, *S.aureus* emerged (Dodds 2017). Resistance against microorganisms is responsible for increase in mortality and morbidity ;by 2050 mortality will rise to 20 million (Watkins and Bonomo 2016). antimicrobials are divided into different groups based on the mechanisms of antimicrobial activity. These groups are; antimicrobials that inhibit the synthesis of the cell wall, inhibit protein synthesis, depolarize the cell membrane, and inhibit metabolic pathways in microorganisms. These mechanisms eem to give a wide ground for the battle against bacteria. But unfortunately, improper use of antibiotics has led to resistance issues (Griffith et al. 2012). More consumption of antibacterial drugs by both humans and animals, improper prescribing of antibiotics and so many other factors have contributed to the issue of resistance (Victor 2011). Resistance and susceptibility are mostly considered as a function of minimum inhibitory concentration (MIC); the minimal concentration of a drug that will inhibit the growth of the bacteria. Resistance may be natural (always expressed in the species) or acquired (naturally occurring genes are expressed after exposure to antibiotics) (Martinez 2014). Against the antimicrobial agent, the pathogenic microorganisms develop resistance in different ways. The mechanism of resistance includes four main categories: (1) drug inactivation; (2) limiting uptake of drugs; (3) active efflux of the drug; (4) modifying a drug target. Natural resistance may limit drug uptake, drug inactivation, and active drug efflux while the mechanisms used by acquired resistance may include drug target modification, drug efflux and drug inactivation. With the alarming situation of drug resistance, we need to combat the pathogens by using other ways like phage therapy (Reygaert 2018). Mechanism is given in Fig. 1.

Mechanism of Action of Bacteriophage

Bacteriophages have a unique specificity characteristic; they only affect a single type of bacterial species. When phages attach to the bacterial cell, they specify the relation between host receptor and phage attachment and stimulate host variations (Drulis-Kawa et al. 2012). Phages are the mandatory intracellular cellular parasites of bacteria that show different modes of action during their life span: lytic cycle, lysogenic cycle, pseudo-lysogenic and recurring illness (Drulis-Kawa et al. 2012).

The lytic mechanism of phage completes in some critical stages and ends when the whole function of bacteria is lost. These steps are:

Adsorption

The assemblage of the phage to the host cell is a highly specified mechanism. The virus only attaches to the receptor-binding site of the bacterial cell. LPS is a frequent phage receptor in Gram-negative bacteria. Other receptors include outer membrane proteins, pili, and flagella (Dowah and Clokie 2018). Peptidoglycan is a receptor for Gram-positive bacteria. Peptidoglycan, often known as murein, is a bacterial cell wall component frequently engaged in bacteriophage adsorption (Bertozzi Silva et al. 2016).

Injection of DNA

Phage releases an enzyme known as lysozyme that produces a hole in the bacteria's cell wall. Phage transfers genetic material into the host cell through this pore, affecting metabolic activities and functions (Gandon 2016).

Production of Viral Protein

After the penetration of viral DNA into the bacterial cytoplasm, the viral DNA holds the complete machinery of bacteria and starts producing proteins and nucleic acid. They also splice the bacterial genome into tiny fragments that lose their normal functions (Barr 2017).

Coat Formation Around Phage Particles

After splicing, viral genome assemblies in the bacteriophage coat and multiple copies in a single bacterial cell are present (Tynecki et al. 2020).

Bursting of Bacteriophage

Phage produces different proteins, including lysins, and murein synthesis inhibitors responsible for the breakage of host cells and efflux of infected virions occurring in the surrounding (Drulis-Kawa et al. 2012) as mentioned in Fig. 2.

The temperate or lysogenic cycle is a mechanism of phage action that suspends virion production. The viral DNA is joined with the bacterial genome and forms a prophage. This prophage does not divide separately to create virion; when the bacterial cells divide through binary fission, they produce the daughter cell containing the viral genome (Obeng et al. 2016). Prophages can help their host bacterial cells survive and flourish through a variety of processes, including protection from contagion, Lysozyme activity and gene

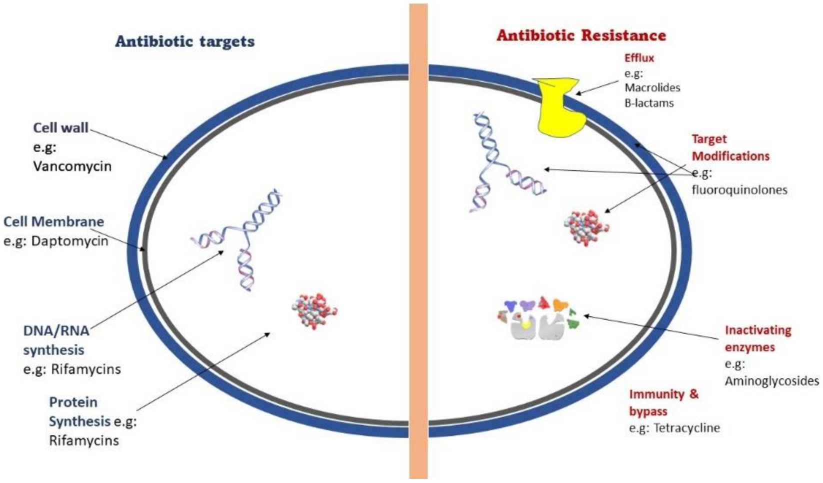

Fig. 1: Antibiotic targets and Antibiotic resistance

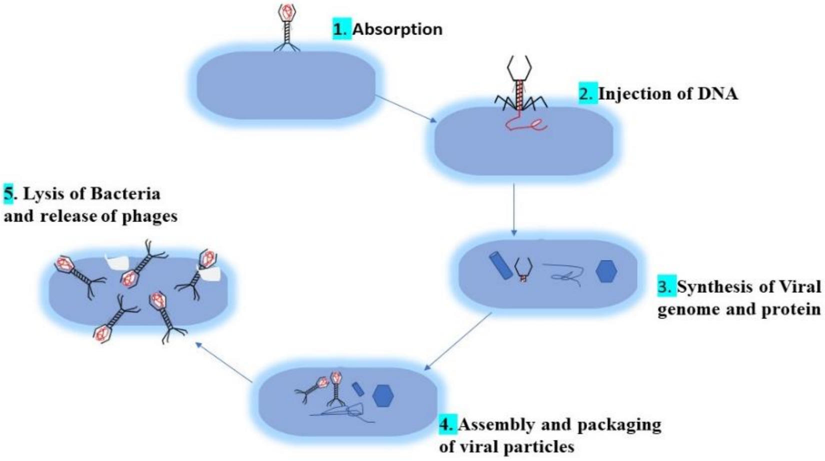

Fig. 2: Mechanism of action of Bacteriophage

transfer improves the suitability of host cell, and fight with bacterial enemy via automatic mechanism and weapons of temperate phage (Mills et al. 2013). Lytic cycle takes about 50 min to complete and releases approximately 100 completed virions (Malys 2012).

Two major genes coded for cI & cro and three promoters namely PL (Left side), PR (Right side) and PRM (Repressor Maintenance) regulate the switching of lytic to lysogenic cycle. PR and PL are strong promoters and bind very efficiently with the RNA polymerase. Prm is a weak promoter that transcribes only the cI genes and requires some kind of activators in the upstream regions. Several studies revealed that, the PL & PR are active during the lytic cycle and the Prm is inactive. On the counterpart, during the lysogenic cycle, the Prm are expressed and the PL & PR remains inactive. These events are regulated by different sets of proteins (Watson et al. 2014).

A modified version of bacteriophage M13 help to insert the gene. They also employed the same procedure with mice infected with *E. coli* intraperitoneally. Mice who were given antibiotics and modified phages at the same time had a higher chance of surviving. Other writers found this strategy as a conventional method used for phage treatment, which results in precise bacterial death (Edgar et al. 2012).

Pseudo lysogeny is another mechanism of phage action in which the bacterial cell develops the stalled virus devoid of genetic cell division (as in lytic action) or phage genome replication synchronized with the cell cycle. As in lysogenization, regular maintenance in the cell line occurs without viral genome degradation, allowing virus development to resume. With the development of favorable conditions within the bacterial cell, this mechanism began as starvation and concluded due to the initiation of lytic growth known as lysogenization (Łoś and Węgrzyn 2012).

Conclusively, when a bacterium is infested by lysogenic phage they inhibit the replication cycle, loses their alteration abilities, and lead to chronic infection. The viral DNA remains in a prophage form for a long period and then the bacterial chromosomes combine this viral DNA and make their new section (Wittebole et al. 2014).

In vitro Applications of Bacteriophages

With the increase in the number of infections and bacteria that are resistant to antibacterial drugs, scientists are forced to find new ways to kill these tenacious pathogens (De Miguel et al. 2020). Various kinds of research reveal the positive effect of phages on bacteria. Some reveal neutral results and or results at all for particular pathogens. With the help of phage-antibiotic synergism against bacterial infections, there are possibilities for enhanced bacterial suppression. The synergy of these two methods will enhance the penetration into biofilms, and the emergence of a new method will help in killing tenacious pathogens. The type of antibiotic with the help of a certain choice of phages and their mixing ratio is a decisive factor in this dual approach. The use of phase-antibiotics is proving useful in the fight against multidrug-resistant bacteria (Łusiak-Szelachowska et al. 2020). Experimental design is of utmost importance. The use of *in vivo* and *in vitro* models with the biofilm is proving useful in finding the most accurate results in the phage-antibiotic combination (Harada et al. 2018). The change in the ratio of the phages and antibiotics helps the researcher with the accurate quantity to come up with the solution. The variation on a smaller scale is impossible to evaluate in real settings (Jamal et al. 2019). That's why researchers are using the techniques to answer the key question of the right mix of phages and antibiotics.

Evaluation of *in vitro* use of *P. aeruginosa* Phages and Antibiotics against Biofilm

CAUTIs (catheter-associated urinary tract infections) are caused by *Proteus mirabilis*, which has the ability to colonize and form biofilms. These biofilms are in the form of crystalline structures and are created on the catheter's surface (Burrowes et al. 2019). The use of the podovirus vB_PmiP_5460 novel variant is found effective against 16 of the 26 Proteus strains in the studies. Another phage, myovirus vB_PmiM_5461targets Proteus strains under study. The dynamic biofilm model revealed the *P. mirabilis* reduction in biofilm for 168 h of catheterization (Melo et al. 2016).

Another study focused on antimicrobial-resistant bacteria and the use of phage therapy with the help of a novel endolysin. The LysPA26 has a lysozyme-like domain that was under study for *Pseudomonas aeruginosa*. This study revealed the ability of LysPA26 to kill the log units of *P. aeruginosa*. The time taken was recorded as per the 4 log units that were killed in 30 minutes. *P. aeruginosa* was also proven effective against biofilm formation and is useful to ward off Gram-negative pathogens (Guo et al. 2017).

Evaluation of in vitro use of *S. aureus* Phages and Antibiotics against Biofilm

Recombinant phage enzymes (lysins) are non-toxic and self-proliferating. They also have the ability to penetrate into biofilms. Lytic phage targeting has reported results mentioned in the table below. Actinomyces phage, Av-1 is the most active agent. This in vitro study revealed that the Actinomyces phage, Av-1 is active in conditions similar to oral cavities (Szafrański et al. 2017). The blockade of co-aggregation reduces the chances of biofilm creation.

E. faecalis is a common pathogen in endocarditis and failure in root canal treatment. The *E. faecium* phage, EFDG1, was obtained from sewage effluents. The electron microscope confirmed the identity of this phage. The association with the Spounavirinae subfamily made this phage able to fight against Gram-positive pathogens. The study revealed that there are no harmful genes in this phage. But its efficacy is against planktonic and biofilm cultures have shown lytic activity against Gram-positive pathogens (Khalifa et al. 2015).

Bacteriophage Control of Foodborne Bacteria

Bacteriophages are the most calculable constituents of the natural microflora in the nutrition manufacturing series which are present from the farm to the trade channel. Phages are extraordinarily steady in these surroundings secondly they are present in the earth, manure, river, farmhouse, and treating herbal wastes, human manure, and foodstuffs (Clokie et al. 2011). Phages are capable to regulate the pathogens as *Listeria monocytogenes*, *Salmonella*, and *Campylobacter, which can exist even in the diverse range of* chilled foods such as fresh fruits, dairy and milk yields. In case of meat it is estimated that it induces effect on poultry meat and other meat products by controlling their deteriorating bacterias which are Pseudomonas spp. and *Brochothrix thermosphacta*. Mostly found in the uncooked chilled meats saved in order to extend the shelf life of it. The shortcomings of biopreservation in using bacteriophages are the narrow range of hosts, the prerequisites to starting this experiment are the infectious goals, phage-resistant mutants, and the possible cause to transfer the genetic material from one bacterium to another to reduce the chances of objectionable characteristics from one bacterial strain to another (Greer and Dilts 2002).

Bacteriophage and its Control on Salmonella

Salmonella spp. is a rod-shaped bacterium specifically gram-negative belonging to the family of *Enterobacteriaceae* which mainly causes diseases or disturbances of the gastrointestinal tract if itincreases beyond the normal range. It can be the source of (Non-typhoidal) gastrointestinal enteritis (inflammation of the intestines) in humans which is spread by consuming contaminated poultry meat and pork. According to the reports, 93.8 million cases (5th to 95th percentile, 61.8–131.6 million) are due to salmonella 85% of all foodborne. (Majowicz et al. 2010; Balasubramanian et al. 2019). So the question arises here how do these animals become infected with such a type of bacteria and what are the possible solutions to eradicate these infections. The method of transmission of salmonella infection to different individuals is spread through the ingesting of foodstuff contaminated with *Salmonella*, particularly from poultry products (Foley et al. 2008). Chickens and turkeys reared are disease-ridden with *Salmonella* infection by polluted fodders, environs around them, or by direct or indirect contact by way of other diseased animals in the herd. (Atterbury et al. 2007). If birds become infected once in their lifespan the infection persists throughout their life asymptomatically or they may induce intestinal infection indications. Moreover, these bacteria may present in the gut of infected animals and forms colony over there which later on spread to other healthy animals by the fecal-oral route(Bonardi 2017, Martinez et al. 2019). this spread can also occur due to the possibility of carcass uncleanness with *Salmonella* during the processing of meat such as slaughtering (Smith et al. 2018), As a result, every step of processing meat from farm to plate increases the possible jeopardy of *infection* prevention can occur only by interrupting the round of infection in the food series prior to the use of the products. In contrast, Phages are the solution which we can add into practice to govern *Salmonella* septicity in animals, which could be helpful to break the chain of infection. According to researchers, there are about 21 myoviruses, and a siphovirus used to exclude *Salmonella* was scrutinized with the purpose seems to emerge a biocontrol scheme to limit the infectivity rate in poultry (Akil and Ahmad 2019).

To control the infections of bacteria, the natural viruses "bacteriophages" are used. Reports show that the bacteriophages can even invade the different strains of salmonella which are resistant to antibiotics MDR (multiple drug resistance).Phages are capable of lysing the strains (Akil and Ahmad 2019; Thanki et al. 2019). So we can easily use the phages to limit the infections of salmonella caused by different strains which are resistant to antibiotics and do not show any effect on them. To improve the functions of phages, phages can be used in combination which can be termed "cocktails" (Chan et al. 2013). Studies showed that these cocktails are efficient upon use and can be helpful to reduce the infectivity of salmonella, as mentioned in Table 1.

In-vivo Applications of Phages

Bacteriophage Therapy in Humans

After the successful introduction of bacteriophage therapy in combination with antibiotics in several in-vivo studies, phage therapy has attained much more attention for its use in in-vivo or human trials. Phage therapy has been used in several clinical trials and ample literature has been published and is now available to have a better understanding of its applications in human studies. The earliest study was in 1919 in Paris, in which a phage preparation was made and ingested by a group of scientists and the chief of the hospital prior to its administration to a young boy to check its safety (Summers 2001). The patient was suffering from severe dysentery and the phage prepared by d'Herelle was ingested by the boy. The results were quite surprising because the patient with dysentery fully recovered after a few days of the treatment and all the symptoms vanished. Similarly, a historical study was carried out which confirmed the effectiveness of phage therapy in the treatment of infectious diseases in humans, but it was published later in 1921 by Richard Bruynoghe and Joseph Maisin. This time several bacteriophages were utilized for the treatment of skin lesions caused by some staphylococcal strains of bacteria (d'Herelle et al. 1922). The infection was suppressed and lowered in intensity within one or two days after the application of the prepared phages into the open wounds and the area around the lesions (Bruynoghe and Maisin 1921). After successful results of previous studies, phage therapy remains a potential agent for treating several bacterial infections including those caused by multi-drug resistant bacteria. A group of scientists worked on evaluating the effectiveness of phage therapy against different bacterial infections and published a series of papers describing the findings of their trials. During 1981-1986, Slopek et al. 1987, applied bacteriophage therapy for the treatment of suppurative bacterial infections to 550 patients. Results showed 90% of the cases with complete recovery while only 38 patients showed varied results. All the patients involved in the study were resistant to several antibiotics and the patients were given phages orally thrice a day (Slopek et al. 1987). The efficacy of phage therapy is also evidence against the biofilms produced by multi-drug resistant Pseudomonas aeruginosa. The treatment strategy involved the use of antibiotic named colistin in combination with bacteriophages, however, the approach of using two different agents made the therapeutic role of phages doubted (Tkhilaishvili et al. 2019). Apart from treating biofilms, phages have also shown satisfying results in the treatment of infections of bone and joints. Successful results were documented while treating the relapsing Staphylococcus aureus-induced prosthetic joint infections with the injection of a group of bacteriophages directly into the debridement site. Similar results were noted during the treatment of multi-drug resistant bacterial-induced septic arthritis and osteomyelitis (FERRY et al. 2022; Nir-Paz et al. 2019). *Klebsiella pneumoniae*, which is capable of producing carbapenemase, plays role in causing urinary tract infections (UTIs) and making it troublesome to treat such kinds of infections. Kuipers et al. 2019, reported the use of a modified bacteriophage combination to treat K. pneumonae-induced UTIs in patients and results showed the obliteration of the colonization in those treated patients (Kuipers et al. 2019). The effectiveness of phages against infections like cerebrospinal meningitis in newborn babies was also found in a study (Stroj et al. 1999). Apart from being effective against several bacterial infections, phage therapy has been proved to be very beneficial in the management of some

Table 1: Biocontrol of pathogens by using phages in food industry

Pathogens	Food production loss	Phages	References
Xanthomonas campestris	Tomatoes	FoX2, FoX6	(Holtappels et al. 2022)
Listeria	Fresh apple, chicken	A511	(Loessner and Busse 1990)
Ralstonia solanacearum	Tobacco	T7likevirus	(Álvarez et al. 2019)
Salmonella enteritidis	Cheese	LPSE1	(Huang et al. 2018)
Escherichia coli	Meat	Cocktail (pp01, e11/2, 24/1c	(O'flynn et al. 2004)
Pseudomonas tolaasii	Mushrooms	LMG 2342^{T}	(Sajben-Nagy et al. 2012)
Campylobacter	Chicken skin	NCTC 12673	(Goode et al. 2003)

kinds of cancer because of its regulatory role in the regulation of TNF-α production and interleukin-6 production by the blood cells (Weber-Dabrowska et al. 2000). Advancements in the use of phages were made in the 20th Century and their hidden potential for treating several bacterial diseases was revealed in multiple clinical trials. A study showed the therapeutic effects of phages in patients suffering from wounds that proved to be difficult to treat. Patients suffering from chronic venous leg ulcers were given treatment with bacteriophages with the intention of killing Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus species. The treatment was continued for 12 weeks, and the control group was given normal saline rather than bacteriophages. The results of the study showed no harmful effects of the use of bacteriophages and proposed the research group conduct phase 2 trials in order to check the efficacy of the phages used (Rhoads et al. 2009). The use of phages continued progressively during the 21st century and phages were utilized for the treatment of chronic rhinosinusitis (CRS) patients. Although antibiotics were being used to cope with the CRS, their inability to tackle biofilm nidus resulted in the reoccurrence of the disease. Mian Li Ooi et al. 2019, used a phage named as phage cocktail AB-SA01 against *Staphylococcus aureus*-induced chronic rhinosinusitis. The phage proved to be efficient and safe for patients with CRS when administered through the intranasal route at a dose of 3 × 109 plaque-forming units (Ooi et al. 2019). Promising results shown by the phage AB-SA01 grabbed the attention of other research groups towards applications of these types of phages in other disease conditions in humans. Similarly, phages found their healing potential in the common skin disorder named acne. Propionibacterium acnes is a gram-positive bacterium that has a vital role in the pathogenesis of this multifactorial disease as its colonization causes inflammation and elevated sebum production by the sebaceous glands of the skin. Although there are some studies showing the effectiveness of phages against several skin infections and their limited ability to kill the acne-causing bacterium, there is no such evidence showing the use of phages for healing human acne (Jończyk-Matysiak et al. 2017).

Bacteriophage Therapy in Animals

Antimicrobial resistance is a threat not only to the medical field but also to the veterinary field because of the increasing ineffectiveness of antibiotics and modifications in pathogenic microorganisms. Due to this escalating resistance towards antimicrobials, alternative strategies are required to cope with the infections in animals in order to ensure the effective treatment of sick animals. Apart from other alternatives to antibiotics like plant extracts, antibodies, and adjuvant vaccines, bacteriophages are also being utilized in place of antibiotics for the treatment of animals, especially food animals. Evidence shows the application of phages in different food products to prevent animals and humans from various bacterial and zoonotic (Tiwari et al. 2014). In case of dogs those are kept as a pet, their abscesses and wounds can be treated with the help of phage therapy instead of conventional antibiotics that have no therapeutic effect now. In a study, the ear infections in dogs caused by multidrug-resistant Pseudomonas aeruginosa were given treatment with the phages and showed positive results as compared to the routinely used antibiotic therapies (Hawkins et al. 2010). Similarly, bacteriophage therapy using a specific type of phage; coliphage, has shown promising results when injected into calves for treatment of E. coli infections and prevented the conditions of meningitis and septicemia (Gigante and Atterbury 2019, Atterbury and Tyson 2021).

Phages are being widely used in the poultry industry to tackle the bacterial disease burden, especially zoonotic infections like salmonellosis. They are also being used prophylactically in poultry birds to combat several infections including colibacillosis, listeriosis, and salmonellosis. In a study, two bacteriophages called EC-Nid and EC-Nidl were collected from the fecal samples of birds and were used to treat the birds affected by salmonellosis and colibacilloses. These phages showed remarkable results against the O1, O2, and O78 strains of *E. coli* and were recommended for use in future studies. Similarly, phages in broiler chickens helped to reduce the bacterial load in the ceca and specifically targeted the colonization of Salmonella enterica species (Oliveira et al. 2010; Atterbury and Barrow 2021). Also, in the newly hatched chicks, the application of a phage named AB2 caused a decrease in the colonization of Salmonella typhimurium in the intestine, ceca, and croup which showed the importance of these phages in improving the health and wellbeing of poultry birds (Kumar et al. 2022). This also shows the role of phages in enhancing and improving public health as poultry meat is a major part of the food chain in many countries. With an increasing population, the protein demands are increasing in most countries and aquaculture is now dominating to compensate and fulfil the protein demands by becoming a major aspect of the food chain. Just like the poultry industry, the aquaculture sector is also suffering substantial losses in production due to antimicrobial resistance and disease burden. phage therapy has been proved to be an effective substitute for antimicrobials to be used in aquaculture because they act against most of the fish-bacterial pathogens including Campylobacter, Salmonella, and Pasteurella piscicida (Emery and Whittington 2004; Connerton et al. 2011). Aquaculture habitats are also very rich in a variety of phages that can be easily isolated and utilized in fish cultures. A phage named Listex P100 has shown evidence for its effectiveness against Listeria monocytogenes and helped to control the settlement of these bacteria as well as fascinating results regarding the control of pyrogens (Park and Nakai 2003).

Limitations in Phage Therapy

Despite the countless benefits and therapeutic uses of bacteriophage therapy in both the veterinary and medical fields, there are still some challenges and limitations that need to be considered while promoting this therapy in place of antibiotics. These include the safety concerns of using phages in humans and animals while administering them either for therapeutic or prophylactic purposes. There is still a need to evaluate the efficacy and safety of these phages in both veterinary and human fields (Khan and Rahman 2022). The important possible considerations while using phage therapy may include the effect of phages on the soft tissues or the alteration in the colonization of the normal microbiota in the species under treatment. Also, they may lead to undesired immunological reactions due to their ability to transduce DNA between various bacteria or by influencing the gene expressions of bacteria (Abedon and Katsaounis 2018; Squires 2018). The other main concern in adopting bacteriophage therapy is the pharmacological aspect of its dosage. Because of their self-replicating nature, these viruses have the ability to increase their numbers exponentially and may exceed the desired dosage (Payne and Jansen 2003). Although there are studies showing the importance of combination therapy like the use of phage cocktails in avoiding resistance development and providing wide-spectrum action, on the other hand, this can increase the difficulties in evaluating the inflammatory effects and the probability of bacteria transferring the genes for resistance development (Payne and Jansen 2018).

As these viruses have both bactericidal and bacteriostatic modes of action in controlling bacterial growth, there are concerns regarding their bactericidal action because it might lead to the development of toxic shock in such individuals (Parracho et al. 2012). However, other studies suggest that it is not a matter of concern as the bactericidal antibiotics have also same mechanism of action but need to be evaluated during the pre-clinical trials of these phages (Dufour et al. 2017). There are also some regulatory issues regarding the accessibility and usage of these phages. There is no proper regulatory framework in many countries of the world that can guide the proper use and availability of these phage products over the counter (Payne and Jansen 2018). However, previous studies show that the use of phages for therapeutic purposes in the medical field is considered a last option when any other treatment option is not available or suitable to treat a patient in a critical condition (Payne and Jansen 2018; Jończyk-Matysiak et al. 2018).

Future Considerations

The limitations or problems using phage therapy require attention to be solved in order to incorporate phage therapy as a successful tool and substitute for antibiotics. The problem of specificity of the phages can be resolved by the establishment of a phage library that contains the data regarding the variety of phages available along with their host ranges (Abedon and Katsaounis 2018).The use of genetic engineering can also prove to help enhance the host range of the phage which can be achieved by targeting the phage part which decides the cloning or binding of the phages with the targeted bacterial site (Lenneman et al. 2021). Furthermore, future research studies should target finding solutions to the existing problems in bacteriophage therapy. Also, the efficacy and safety concerns of phages should be tested in future research studies. To make phage therapy successful, the policies regarding phage therapy should be developed properly in collaboration with government authorities and developing countries around the globe.

Conclusion

Antibiotics have been considered an important achievement against infectious diseases as mortality and morbidity were causing a huge loss to the economy due to such diseases. However, later the improper use of antimicrobial agents against infectious diseases led to the development of resistance in many bacteria against these antimicrobials. Antibiotics target bacteria in different ways like inhibition of their cell wall, protein synthesis, inhibiting the metabolic pathways, and depolarization of cell membrane. Most of the time antibiotic resistance developed due to active efflux of drugs, target modification, and limiting uptake of drugs. Although many other alternatives to antibiotics are being introduced and implied against various bacteria, bacteriophage therapy is one of the important choices to combat bacteria. Phage therapy has been used for a century and due to antimicrobial resistance, page therapy has gotten more recognition recently. It is being practiced as an emerging alternate strategy to combat various pathogens in both the medical and veterinary sectors. There is no doubt that page therapy is an attractive solution against pathogenic bacteria, but the efficacy and precautions of using these phages need to be evaluated in future research. Moreover, the issues regarding the regulation and use of this therapy in medical sciences should be solved and proper legislation should be done to avoid the issues of regulation in many countries of the world.

REFERENCES

Abedon ST and Katsaounis TI, 2018. "Basic phage mathematics." Bacteriophages 2018: 3-30.

Akil L and Ahmad HA, 2019. "Quantitative risk assessment model of human salmonellosis resulting from consumption of broiler chicken." Diseases **7**(1): 19.

Álvarez B et al., 2019. "Biocontrol of the major plant pathogen Ralstonia solanacearum in irrigation water and host plants by novel waterborne lytic bacteriophages." Frontiers in Microbiology 10: 2813.

Aminov RI, 2010. "A brief history of the antibiotic era: lessons learned and challenges for the future." Frontiers in Microbiology 1: 134.

Atterbury RJ and Barrow PA, 2021. "The Use of Bacteriophages in Veterinary Therapy." Bacteriophages: Biology, Technology, Therapy 2021: 953-987.

Atterbury RJ and Tyson J, 2021. "Predatory bacteria as living antibiotics–where are we now?" Microbiology 167(1): 001025.

Atterbury RJ et al., 2007. "Bacteriophage therapy to reduce Salmonella colonization of broiler chickens." Applied and Environmental Microbiology 73(14): 4543-4549.

Balasubramanian R et al., 2019. "The global burden and epidemiology of invasive non-typhoidal Salmonella infections." Human Vaccines and Immunotherapeutics 15(6): 1421-1426.

Barr JJ, 2017. "A bacteriophages journey through the human body." Immunological Reviews 279(1): 106-122.

Bertozzi Silva J et al., 2016. "Host receptors for bacteriophage adsorption." FEMS Microbiology Letters 363(4): 002.

Bonardi S, 2017. "Salmonella in the pork production chain and its impact on human health in the European Union." Epidemiology and Infection 145(8): 1513-1526.

Bruynoghe R and Maisin J, 1921. "Therapeutic trials using bacteriophage." Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales 85: 1120-1121.

Burrowes BH et al., 2019. "Directed in vitro evolution of therapeutic bacteriophages: the Appelmans protocol." Viruses 11(3): 241.

Bush LM, 2011. "Best alternative to vancomycin for serious methicillin-resistant Staphylococcus aureus infections: let's just say it." Clinical Infectious Diseases 53(9): 965-966.

Chan BK et al., 2013. "Phage cocktails and the future of phage therapy." Future Microbiology 8(6): 769-783.

Chanishvili N, 2012. "Phage therapy—history from Twort and d'Herelle through Soviet experience to current approaches." Advances in Virus Research 83: 3-40.

Clardy J and Fischbach M, 2009. The natural history of antibiotics." Current Biology 19: 1-8.

Clokie MR et al., 2011. "Phages in nature." Bacteriophage 1(1): 31-45.

Connerton P et al., 2011. "Campylobacter bacteriophages and bacteriophage therapy." Journal of Applied Microbiology 111(2): 255-265.

d'Herelle F et al., 1922. "Discussion on the bacteriophage (bacteriolysin)." The British Medical Journal 2011: 289-299.

de Miguel T et al., 2020. "Bacteriophages and lysins as possible alternatives to treat antibiotic-resistant urinary tract infections." Antibiotics 9(8): 466.

Dodds DR, 2017. "Antibiotic resistance: A current epilogue." Biochemical Pharmacology 134: 139-146.

Dowah AS and Clokie MR, 2018. "Review of the nature, diversity and structure of bacteriophage receptor binding proteins that target Gram-positive bacteria." Biophysical Reviews 10(2): 535-542.

Drulis-Kawa Z et al., 2012. "Learning from bacteriophages-advantages and limitations of phage and phage-encoded protein applications." Current Protein and Peptide Science 13(8): 699-722.

Dufour N et al., 2017. "The lysis of pathogenic Escherichia coli by bacteriophages releases less endotoxin than by β-lactams." Clinical Infectious Diseases 64(11): 1582-1588.

Edgar R et al., 2012. "Reversing bacterial resistance to antibiotics by phage-mediated delivery of dominant sensitive genes." Applied and Environmental Microbiology 78(3): 744-751.

Emery DL and Whittington RJ, 2004. "An evaluation of mycophage therapy, chemotherapy and vaccination for control of Mycobacterium avium subsp. paratuberculosis infection." Veterinary Microbiology 104(3-4): 143-155.

Ferry T et al., 2022. "Personalized bacteriophage therapy to treat pandrug-resistant spinal P. aeruginosa infection."

Foley S et al., 2008. "Salmonella challenges: prevalence in swine and poultry and potential pathogenicity of such isolates." Journal of Animal Science 86(14): E149-E162.

Furfaro LL et al., 2018. "Bacteriophage therapy: clinical trials and regulatory hurdles." Frontiers in Cellular and Infection Microbiology 8: 376.

Gandon S, 2016. "Why be temperate: lessons from bacteriophage λ." Trends in microbiology 24(5): 356-365.

Gigante A and Atterbury RJ, 2019. "Veterinary use of bacteriophage therapy in intensively-reared livestock." Virology journal 16(1): 1-9.

Goode D et al., 2003. "Reduction of experimental Salmonella and Campylobacter contamination of chicken skin by application of lytic bacteriophages." Applied and Environmental Microbiology 69(8): 5032-5036.

Górski A et al., 2018. "Phage therapy in prostatitis: Recent prospects." Frontiers in Microbiology 9: 1434.

Greer GG and Dilts BD, 2002. "Control of Brochothrix thermosphacta spoilage of pork adipose tissue using bacteriophages." Journal of Food Protection 65(5): 861-863.

Griffith M et al., 2012. "Antimicrobial stewardship programs: methods of operation and suggested outcomes." Expert Review of Anti-infective Therapy 10(1): 63-73.

Guo M et al., 2017. "A novel antimicrobial endolysin, LysPA26, against Pseudomonas aeruginosa." Frontiers in Microbiology 8: 293.

Harada LK et al., 2018. "Biotechnological applications of bacteriophages: State of the art." Microbiological Research 212: 38-58.

Hawkins C et al., 2010. "Topical treatment of Pseudomonas aeruginosa otitis of dogs with a bacteriophage mixture: a before/after clinical trial." Veterinary Microbiology 146(3-4): 309-313.

Holtappels D et al., 2022. "The potential of bacteriophages to control Xanthomonas campestris pv. campestris at different stages of disease development." Microbial Biotechnology.

Huang C et al., 2018. "Isolation, characterization, and application of bacteriophage LPSE1 against Salmonella enterica in ready to eat (RTE) foods." Frontiers in Microbiology 9: 1046.

Jamal M et al., 2019. "Bacteriophages: an overview of the control strategies against multiple bacterial infections in different fields." Journal of Basic Microbiology 59(2): 123-133.

Jończyk-Matysiak E et al., 2017. "Prospects of phage application in the treatment of acne caused by Propionibacterium acnes." Frontiers in Microbiology 8: 164.

Khalifa L et al., 2015. "Targeting Enterococcus faecalis biofilms with phage therapy." Applied and Environmental Microbiology 81(8): 2696-2705.

Khan MAS and Rahman SR, 2022. "Use of Phages to Treat Antimicrobial-Resistant Salmonella Infections in Poultry." Veterinary Sciences 9(8): 438.

Kuipers S et al., 2019. "A Dutch case report of successful treatment of chronic relapsing urinary tract infection with bacteriophages in a renal transplant patient." Antimicrobial agents and Chemotherapy 64(1): 01281-01219.

Kumar A et al., 2022. "Isolation and characterization of Salmonella phages and phage cocktail mediated biocontrol of Salmonella enterica serovar Typhimurium in chicken meat." Lebensmittel-Wissenschaft and Technologie 155: 112957.

Lenneman BR et al., 2021. "Enhancing phage therapy through synthetic biology and genome engineering." Current Opinion in Biotechnology 68: 151-159.

Levy SB, 1992. From tragedy the antibiotic age is born. The Antibiotic Paradox, Springer 1992: 1-12.

Levy SB and Marshall B, 2004. "Antibacterial resistance worldwide: causes, challenges and responses." Nature Medicine 10(12): S122-S129.

Loessner MJ and Busse M, 1990. "Bacteriophage typing of Listeria species." Applied and Environmental Microbiology 56(6): 1912-1918.

Łoś M and Węgrzyn G, 2012. "Pseudolysogeny." Advances in virus research 82: 339-349.

Łusiak-Szelachowska M et al., 2020. "Bacteriophages and lysins in biofilm control." Virologica Sinica 35(2): 125-133.

Majowicz SE et al., 2010. "International Collaboration on Enteric Disease "Burden of Illness" Studies. 2010." The global burden of nontyphoidal Salmonella gastroenteritis. Clinical Infectious Diseases 50(6): 882-889.

Malys N, 2012. "Shine-Dalgarno sequence of bacteriophage T4: GAGG prevails in early genes." Molecular Biology Reports 39(1): 33-39.

Martinez JL, 2014. "General principles of antibiotic resistance in bacteria." Drug Discovery Today: Technologies 11: 33-39.

Martinez MN et al., 2019. "Questions associated with the development of novel drugs intended for the treatment of bacterial infections in veterinary species." The Veterinary Journal 248: 79-85.

Melo LD et al., 2016. "Development of a phage cocktail to control Proteus mirabilis catheter-associated urinary tract infections." Frontiers in microbiology 7: 1024.

Mills S et al., 2013. "Movers and shakers: influence of bacteriophages in shaping the mammalian gut microbiota." Gut Microbes 4(1): 4-16.

Nir-Paz R et al., 2019. "Successful treatment of antibiotic-resistant, poly-microbial bone infection with bacteriophages and antibiotics combination." Clinical Infectious Diseases 69(11): 2015-2018.

O'flynn G et al., 2004. "Evaluation of a cocktail of three bacteriophages for biocontrol of Escherichia coli O157: H7." Applied and Environmental Microbiology 70(6): 3417-3424.

Obeng N et al., 2016. "The significance of mutualistic phages for bacterial ecology and evolution." Trends in Microbiology 24(6): 440-449.

Oliveira A et al., 2010. "In vivo efficiency evaluation of a phage cocktail in controlling severe colibacillosis in confined conditions and experimental poultry houses." Veterinary Microbiology 146(3-4): 303-308.

Ooi ML et al., 2019. "Safety and tolerability of bacteriophage therapy for chronic rhinosinusitis due to Staphylococcus aureus." JAMA Otolaryngology–Head and Neck Surgery 145(8): 723-729.

Park SC and Nakai T, 2003. "Bacteriophage control of Pseudomonas plecoglossicida infection in ayu Plecoglossus altivelis." Diseases of Aquatic Organisms 53(1): 33-39.

Parracho HM et al., 2012. "The role of regulated clinical trials in the development of bacteriophage therapeutics." Journal of molecular and genetic medicine: an International Journal of Biomedical Research 6: 279.

Payne RJ and Jansen VA, 2003. "Pharmacokinetic principles of bacteriophage therapy." Clinical Pharmacokinetics 42(4): 315-325.

Reygaert W, 2018. "Department of Biomedical Sciences, Oakland University William Beaumont School of Medicine, Rochester, MI, USA, An overview of the antimicrobial resistance mechanisms of bacteria." AIMS Microbiology 4: 482-501.

Rhoads D et al., 2009. "Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial." Journal of Wound Care 18(6): 237-243.

Sajben-Nagy E et al., 2012. "Isolation of new Pseudomonas tolaasii bacteriophages and genomic investigation of the lytic phage BF7." FEMS Microbiology Letters 332(2): 162-169.

WHO Expert Committee, 2014 on the Selection, Use of Essential Medicines, World Health Organization. The Selection and Use of Essential Medicines: Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). World Health Organization

Slopek S et al., 1987. "Results of bacteriophage treatment of suppurative bacterial infections in the years 1981-1986." Archivum Immunologiae et Therapiae Experimentalis 35(5): 569-583.

Smith PW et al., 2012. "Infection control through the ages." American Journal of Infection Control 40(1): 35-42.

Smith R et al., 2018. "How do pig farms maintain low Salmonella prevalence: a case-control study." Epidemiology and Infection 146(15): 1909-1915.

Squires R, 2018. "Bacteriophage therapy for management of bacterial infections in veterinary practice: what was once old is new again." New Zealand Veterinary Journal 66(5): 229-235.

Stroj L et al., 1999. "Successful treatment with bacteriophage in purulent cerebrospinal meningitis in a newborn." Neurologia i Neurochirurgia Polska 33(3): 693-698.

Sulakvelidze A and Alavidze Z, 2001. "Morris JGJr." Bacteriophage therapy. Antimicrobe Agents Chemotherapy 45: 649-659.

Summers WC, 2001. "Bacteriophage therapy." Annual Review of Microbiology 55: 437.

Szafrański SP et al., 2017. "The use of bacteriophages to biocontrol oral biofilms." Journal of Biotechnology 250: 29-44.

Thanki AM et al., 2019. "Genomic characterization of jumbo Salmonella phages that effectively target United Kingdom pig-associated Salmonella serotypes." Frontiers in Microbiology 10: 1491.

Tiwari R et al., 2014. "Bacteriophage therapy for safeguarding animal and human health: a review." Pakistan Journal of Biological Sciences: PJBS 17(3): 301-315.

Tkhilaishvili T et al., 2019. "Bacteriophages as adjuvant to antibiotics for the treatment of periprosthetic joint infection caused by multidrug-resistant Pseudomonas aeruginosa." Antimicrobial Agents and Chemotherapy 64(1): 00924-00919.

Tynecki P et al., 2020. "PhageAI-bacteriophage life cycle recognition with machine learning and natural language processing." bioRxiv.

Victor LY, 2011. "Guidelines for hospital-acquired pneumonia and health-care-associated pneumonia: a vulnerability, a pitfall, and a fatal flaw." The Lancet Infectious Diseases 11(3): 248-252.

Watkins RR and Bonomo RA, 2016. "Overview: global and local impact of antibiotic resistance." Infectious Disease Clinics 30(2): 313-322.

Watson JD et al., 2014. Molecular biology of the gene, Tokyo Denki University Press.

Weber-Dąbrowska B et al., 2001. "Bacteriophage therapy of bacterial infections: an update of our institute's experience." Inflammation 2001: 201-209.

Weber-Dabrowska B et al., 2000. "Effective phage therapy is associated with normalization of cytokine production by blood cell cultures." Archivum Immunologiae et Therapiae Experimentalis 48(1): 31-37.

Wittebole X et al., 2014. "A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens." Virulence 5(1): 226-235.

25

Strategies and Advancements for Control of Vector Borne Diseases of Public Health Concern

AUTHORS DETAIL

Zurisha Rani [1], Asghar Abbas [2], Zohaib Saeed [1], Hafiza Amna Zaheer [1], Rao Zahid Abbas [1]

[1] Department of Parasitology, University of Agriculture Faisalabad, Pakistan
[2] Faculty of Veterinary and Animal Sciences, MNS-University of Agriculture, Multan, Pakistan
*Corresponding author: zurisha12@gmail.com

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INTRODUCTION

Different types of pathogens such as snails, triatomine bugs, ticks and mosquitoes, lice, flies and arthropods (Dewar 2022) causes a major global health concern. Table 1 shows the etiological agents and vector for various diseases important regarding public health concern. According to WHO (2017), various infectious diseases such as leshmaniasis, dengue, lymphatic filariasis (LF), malaria and yellow fever causes 80 % threats, however, lyme disease, malaria and dengue is a major threat and causes an increase in death rate @ 700,000 deaths per anum via WHO 2020. Moreover, more than 2 vector borne diseases (VBD's) are found in different places are living in nature and causing a significant role i.e., up to 17% in spreading infectious diseases globally (WHO 2020).
There are vector control method available in order to reduce down the infection by different vectors. In addition to that, it is considered as the only method to control dengue as its licensed vaccine is not used commonly due to multiple reasons (Sridhar et al. 2018). However, Chikungunya, West Nile fever and Zika vaccines are used in order to protect the population by decreasing the interaction of human population with various kind of pathogens (Wilson et al. 2020).
There are two categories of vector control methods i.e., chemical and non-chemical tools. These are depending on various developmental stages i.e., the tools may target developmental and adult stages. To manipulate immature stages, aquatic habitats were used as a platform to use biological larvicides and chemicals while for adults, vectors are used for indoor and space spraying, reduction in host-vector interaction by using different kinds of repellants, house screening and bed nets. In addition to this, some methods such as alteration in the genetic make-up of mosquitoes and eave tube netting coated with insecticide drug are still under consideration (Table 2).
According to WHO report (2015), chemical methods are still in use as no vaccines are available for the control of vector borne diseases (VBDs). In order to reduce vector population different chemicals are being used such as chemical fogging to control the *Culex* spp. and *Aedes* spp. while for the control of malaria, insecticides and sprays are still in use (Newby et al. 2021). As per different calculations 1.6 billion pyrethroid bed nets in Africa and 1.8 billion in America were provided to the people (Malaria 2015). Due to the excessive use of these insecticides, resistance is developed in them for various vectors including WHO-approved insecticides around the globe (Moyes et al. 2017). According to a WHO report (2012), Malaria-endemic countries are showing up to 90% of resistance to *Anopheles* while up to 32% resistance is being shown by four other drugs i.e., organochlorines, carbamates, pyrethroids, and organophosphate in remaining countries. This continuous increase in the resistance development against targeted insecticides is alarming as it will reduce the affectivity of VBDs controlling products.

Environmental Management for the Control of VBDs

In order to control VBDs, vital tool is the environmental management. So, there is a need to understand the complete behavioral ecology of vector before use of insecticides. According to Wilson et al. (2020), the breeding areas of vectors which are nearest to human population should be completely destroyed, altered or removed in order to reduce its connection with humans. Moreover, environmental modification, alteration in human habitats and manipulation of environment are the part of these strategies as well. These changes can significantly reduce the vector breeding by destructing water bodies and breeding sites, flushing streams and most importantly introducing vector eaters (predators) over the site. Ecological strategies are different for different vectors for example, for the control of *Anopheles* (*A.*) *funestus*, manipulation of large water body can be done while for *A. gambiae*, drying of small water bodies is sufficient (Kahamba et al. 2022).
Apart from above mentioned strategies, many other practices are efficient in reducing VBDs such as eave tubes (Sternberg et al. 2021), use of nets on doors and windows (Kirby et al. 2009), insecticide coated ribbons (Kaindoa et al. 2021) and medicated eave baffles (Killeen et al. 2017).

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Table 1: Various Vector Borne diseases, etiological agents and vectors

Diseases	Etiological agent	Vector	Pathogen	Reference
Sleeping sickness	*Trypanosoma brucei*	Tsetse fly	Protozoa	Dewar et al. 2022
Leishmaniasis	*Lieshmania. martiniquensis*	Sand fly		Singh et al. 2021
Malaria	*Plasmodium malariae, P. ovale, P. vivax. P. falciparum*	*Anopheles funestus, Anopheles arabiensis*		Girma et al. 2021
Onchocerciasis	*Onchocerca volvulus*	Black fly	Nematodes	Remme et al. 2021
Lymphatic filariasis	Filarial nematodes	*Aedes, Anopheles, Culex* mosquitoes	(Helminths)	Bagiwa et al. 2022
Tularaemia	*F. tularensis*	Ticks	Bacteria	Sormunen et al. 2021
Tsutsugamushi disease	*Orientia tsutsugamushi*	Lice		Xiang et al. 2022
Dengue	Dengue virus (DENV)			Balakumar et al. 2022
Yellow fever	Yellow fever virus			Krivosheina et al. 2021
Zika disease	Zika disease virus			Yamaoka et al. 2021
West Nile fever	West Nile Virus (WNV)	*Culex*		Shin et al. 2022

Table 2: Possible approaches to control mosquito vectors

Type of Control	Life stage of Vector	Methods/tools to control vector	Examples	Mechanism of Action	References
Chemical	Larvae	Larvicides	● Pyriproxyfen ● Bacillus thuringiensis var. israelensis ● Temephos	Provide protection against dengue and disturb the endocrine and nervous system of the insect	Badolo et al. 2022
	Adult	Insecticide treated bed net (ITNs)	● Deltamethrin ITNs ● Permethrin ITNs	Provide defense from malria, lymphatic filarisis and Leismaniasis	Lindsay et al. 2021, Madgwick and Kanitz 2022
		Insecticide treated clothing	● Permethrin	Provides community protection	Vang et al. 2022
		Indoor Insecticides spray	● Carbametes ● Synthetic pyrethroid ● Organophosphates	For the control of *aedes* and *aegypti*	Ritchie et al. 2021, Dulacha 2022
		Space spraying		Used for control of *Anopheles* and *aedes*	Van den Berg et al. 2021
		Aerial Spray of Insecticides		Vector habitat shift	Matthews 2022
		Cattle treated with insecticides	● Pyrethroids	For tsetse fly control	Ruiz-Castillo 2021
		Chemical repellents	● Transfluthrin eave coils	Reduces attacks of vector attacks	Odintsova and Lipina 2022
Non-Chemical methods	Larvae	Modification of vector habitat	● Polystyrene beads	Modification of habitat with drying and drainage of water.	Jung et al. 2021
		Natural predator fish for vector larvae		Biological control for vector	Doloi 2021
		Manipulation of habitat		Regular cleaning and maintenance of domestic containers, Expose areas to the sun light.	Christian et al. 2021
		Microbial larvicides	● *B. sphaericus* ● *B. thuringiensis*		Viana et al. 2021
	Adults	Screening of Houses		Use door and window screening	Lindsay et al. 2021
		Electro-Mechanical MosquitoTraps	● Electrical systems of mosquito trapping ● Sticky adulticidal oviposition trapping systems	Diseases of mosquito origin	James et al. 2022

By these methods, there is a need of low quantity of insecticides as compared to others (odor-bait traps) and are thought to be more effective practice that is capable of reducing up to 40% malaria outbreak in western parts of Kenya (Msugupakulya et al. 2020). Ovitrap is also considered as an effective tool for control of *Aedes* mosquitoes (De Las Llagas et al. 2016).

Community engagement plays very crucial role in the successful implementation of any control method for VBDs (Thizy et al. 2019). For this, there is a need of local body involvement for the identification and modification of targeted areas as happened in Tanzania outbreak (Lupenza et al. 2021). In the same way, farmers are recommended to use fertilizers in order to treat larvicides that will control mosquitoes. Moreover, there is a need to start different campaigns to give knowledge and awareness among people of different communities (Thizy et al. 2019).

Chemical Methods to Control Vectors

The eradication of VBDs is heavily dependent over vector control through eco-management and the insecticide use

(Wilson et al. 2020). Insecticide-treated nets, indoor insecticide coating (Residual spraying), space spraying, and use of spatial repellents are all part of the chemical control strategy (Wilson et al. 2020).

Indoor and Outdoor Insecticide Spraying

In high-risk locations for VBDs, indoor insecticide residual spraying (IRS) is regarded as the cornerstone of the chemical control technique (Huda et al. 2019). This technique involves applying several residual insecticides to the walls of homes and other animal husbandry facilities. The effectiveness of this system is reliant on several factors including the quality of the pesticide used to cover the wall, the type of wall, and the local climate (Faraj et al. 2013).

IRS along with dichlorodiphenyltrichloroethane (DDT) considerably controls the malaria and also effectively controlled the transmission of leishmaniasis in various countries such as Greece, India, Italy and Iran. Using various organochlorine derivatives has led to resistance in vectors, as the use of DDT for sand fly has been restricted due to the harm to human health (Dhiman and Yadav 2016).

An innovative technique called insecticide treated durable wall lining (DWL) is developed to counteract the effects of insecticide that are frequently present in IRS. In DWL, the surface of the inside walls is covered with a polyethene net sprayed with pesticide (Messenger and Rowland 2017). The most efficient strategy for reducing the prevalence of *Phlebotomus* (*P.*) *argentipes* in southern Asian nations is DWL, which is preferred over IRS (Huda et al. 2019). With a single application of deltamethrin, Outdoor Insecticide spraying controlled the *Platanus* (*P.*) *Orientalis* sand fly population up to 83-99% (Elnaiem et al. 2020).

Vector Repellents

“Repellent” originated from the Latin word "repellere," which means “to refuse” (Pugliese et al. 2021). The repellents are typically offered in a variety of formats, including candles, coils, and sprays, primarily used to lessen vector interaction with the human population. The repellents release volatile compounds into the atmosphere, which alter the behavior of the vector and lessen the infection transmission (Achee et al. 2012). The amount of the chemical employed to control the vector is crucial (Grieco et al. 2007), because transfluthrin and metofluthrin are among volatile compounds but their ability to repel and kill depends on their airborne concentration (Ritchie and Devine 2013). Several plants, including *Ricinus communis*, *Geranium* species, and *Solanum jasminoides*, have active components that are evaluated in experimental settings to deter sand flies (Dinesh et al. 2014).

Attractive but Toxic Sugar Baits (ATSB)

These ATSBs target vector populations in both indoor and outdoor settings that exhibit sugar-seeking behavior. These lures are effective for killing adult males and females directly (Saghafipour et al. 2017). ATSBs can be applied in a variety of ways, such as a spray on vegetation, a coated barrier fence surrounding regions of dense habitation, and at bait stations. It delivers a great deal of beneficial outcomes in each kind. 1% boric acid was employed as ATSB in Israel and Iran, where it decreased the *Phlebotomus papatasi* population by 90% (Saghafipour et al. 2016).

Insecticide Treated Materials (ITMs)

ITMs offer exterior shield from the vector bite. The general public, especially workers and military personnel, wear clothing that has been treated with various pesticides such as Permethrin because it has the potential to repel various vectors and poses a lower danger to human health (Banks et al. 2014). ITMs have been shown to be beneficial against VBDs like leishmaniasis and malaria. Richards et al. (2018) and Mitchell et al. (2020) discovered that permethrin-treated clothes (PTCs) are also effective against mosquito bites and tick bites in the United States. In a lab setting, it offers a defense against *A. aegypti* (Faulde 2018), and when combined with PTC, it significantly decreased *A. aegypti* biting in school-aged childrens (Achee et al. 2019). However, other factors hampered the effectiveness of PTC, such as the fact that it washes out of the cloth and is rapidly degraded by UV light (Vang et al. 2022).

Insecticide Treated Bed Nets (ITBN)

ITBNs have vital importance for prevention and control of malaria in most parts of Africa (Lindblade et al. 2015). These nets act as a physical barrier and shield users from vector bites. In order to reduce the spread of malaria in high-risk areas, WHO also suggest the use of ITBNs (Linn et al. 2019). Due to their low hazardous risk, pyrethroids are the only pesticide that can be used on ITBNs (Duchon et al. 2014). The first vector to exhibit pyrethroid resistance was *Anopheles gambiae*. Later, *Anopheles funestus* was also revealed to have it, and both of these resilient vectors subsequently spread in the population (Gnankine and Bassole 2017). Leishmaniasis transmission was reduced by 98% for a year when ITBNs were used (Emami et al. 2009). In pyrethroid-resistant regions, like in Turkey, where *Phlebotomus tobbi* biting was protected up to 92% by co-treated nets with piperonyl butoxide (Gunay et al. 2014). However, in India and Nepal, the deployment of these nets had a negative influence on the spread of diseases (Picado et al. 2010). This may be because of multiple factors, including changing vector feeding behavior, operational issues, and a lack of community involvement (Banjara et al. 2019)

Chemical control strategies are used to prevent vector-induced chemical accumulation in the food chain as well as vector resistance, while biological control approaches are safe and beneficial to the environment (Dewar 2022).

Biological Control

Insecticides reduce vector populations, but they also pose a risk to the general public and unintended species. In contrast, biological agents are safe over the long term and have less damaging effects on people, animals, and the environment. Different biological agents, including parasitoid wasps, bacteria (*Bacillus thuringiensis*), birds that feed on insectivores, deuteromycete fungi (*Beauvaria bassiana*, *Metarhizium anisopliae*), nematodes, and fish, can be utilized in biological management (Ramzan et al. 2021).
Biological control of mosquitoes can be done by using natural enemies such as use of fish that eat the larvae in the water bodies. Ghosh and Dash (2007) described the larvivourous feeding behavior 315 fish that can be used for the control of malaria. The number of larval breeding sites in Western Rajasthan reduced by 99% and 97%, respectively, after the introduction of fish, *Gambusia affanis* in diggies and sumpwells (Singh et al. 2022).
Additionally, dragonflies can be useful in the management of mosquitoes. Dragonfly and damselfly are regarded as effective predators for the control of *Aedes* larvae (Venkatesh and Tyagi 2013). Similarly, *Tholymis tillarga*, *Anax indicus*, and *Pantala flavescens* can be utilized to treat *Aedes aegypti* because they were successful in lab tests (Samanmali et al. 2018).
Bacillus (*B.*) *thuringiensis* was successfully employed to control mosquitoes throughout Europe (Bruhl et al. 2020). According to Bohari et al. (2020), the *B. thuringiensis israelensis* strain has potential to effectively lower the vector population when used in conjunction with other vector control techniques. Shaw et al. (2016) claim that Wolbachia has the capacity to change an insect's ecology, physiology, and behaviour, which would reduce the spread of infectious diseases. In numerous research investigations, Wolbachia has also been cited as an efficient biological control technique for diseases transmitted by mosquitoes (Bian et al. 2013). Helmeted guineafowl is a bird which can be utilized for controlling the spread of ticks and tick-borne diseases (Ramzan et al. 2021).

Botanicals for Vector Control

Plants have adulticidal, larvicidal, insecticidal and repellent potential (Isman 2020). These are widely used in different parts of the world. Plant based extracts that are used in insecticides are safe for the environment and the non-targeted animals. Such insecticides have been widely used for the control of insects for many years (Belmain et al. 2012) because such type of bio-peticides are safe, reduced risk of resistance and plant extracts have repellent property as well (Tembo et al. 2018). Plant extracts for the control of insects are basically prepared from the weed species that grow in the field as compared to the synthetic insecticides in developing countries. Biopesticides have been used for centuries but still its use is less than 1% over the globe (Isman 2017).

The three families Lamiaceae, Apiacea, and Asteraceae are employed to manipulate habitat and have insecticidal capability. The tested plants of these families have 39.3%, 72.2%,25.7% insecticidal capability, respectively and can be used for habitat manipulation (Amoabeng et al. 2019). According to Boulogne et al. (2012), 656 species out of 110 families are well reported for having insecticidal properties. Researchers have focused on using plant repellant as an effective alternative over chemical solutions to control arthropods such as arachnids (Ellse et al. 2016; Lee et al. 2018) and mosquitoes (Tisgratog et al. 2016; Pavela et al. 2019).

Genetically Modified Vector Species

By using different controlling interventions for the VBDs, there is still significant mortality of human population from such diseases. Genetic control (GC) has now drawn the attention of the researchers as alternative method that depends on two factors: 1) renewal of the vectors with modified disease refractory mosquitoes, 2) Introduction of new modified mosquitoes with lethal gene that will overpower the target vector population (Wilke and Marrelli 2015). First technique includes the sterilized insect technique (SIT) while the other one is gene drive. SIT further includes the radiation induced male sterility, *Wolbachia*-mediated cytoplasmic incompatibility (CI) while the gene drive includes the homin endonuclease, Medea based gene drive and modified midgut bacteria (Tyagi 2016). Recently, it was observed that CRISPR/Cas9-based gene drive is effective tool that can spread the target gene in all the mosquitoes, yeast and fruit flies' population in the laboratory and this strategy can also eradicate the VBDs (Collins 2018). The majority of these techniques are still in their infancy because it takes a lot of mosquitoes to be released at different times and locations in order to suppress, diminish, and replace the vector population.

Vaccine Development against VBDs

Development of effective vaccine for the control of VBDs is quite challenging. It is evidenced by the point that as of 2019, only two vaccines have been approved by the WHO for the control of yellow fever and Japanese encephalitis virus (JEV) (Manning and Cantaert 2019). Moreover, one more vaccine was recently approved for malaria (*P. falciparum*) that need four doses of vaccines but provides only 36 % of efficient results (Schuerman 2019). Struggles for the development of safe and effective vaccine for dengue have been disturbed by the cross reaction of antibodies in serotypes and unsatisfactory immune response (Halstead 1978). Approved vaccine for the dengue can only be used strictly for dengue experienced patients with above 9 years of age (WHO 2018). The licensed vaccine for Lyme disease has been now removed from the market (Nuttall 1999). For the control of VBDs, use of effective and safe vaccines are the best defense. However, it is combined complexity of the various microbes of host, the dermal microenvironment and the vector that causes the challenge for the development of effective vaccine.

Conclusion

Vector-borne diseases such as dengue, leishmaniasis, lymphatic filariasis and Malaria etc. induced a significant burden of morbidity and mortality around the globe, especially in developing countries. VBD's is an international human health concern that needs effective interventions for their control. The principal control method of VBD is vector control. Different chemical and non-chemical methods are used to reduce vector-human contact. The use of chemicals results in the accumulation of different insecticides in the food chain and also induces resistance in the vector while the non-chemical (biological control) methods are environmental friendly and safe for the untargeted species. Due to the lack of vaccines for different VBDs, we can only rely on the existing interventions. But still, we need to develop alternative and effective strategies for the control of next-generation vectors by using traps, repellents, modified vectors, etc. Among these vector-controlling measures, health education and public awareness are effective and valuable tools for long-term vector control intervention.

REFERENCES

Achee NL et al., 2012. Spatial repellents: from discovery and development to evidence-based validation. Malaria Journal 11(1): 1-9.

Achee NL et al., 2019. Alternative strategies for mosquito-borne arbovirus control. PLoS Neglected Tropical Diseases 13(1): 0006822.

Amoabeng BW et al., 2019. Natural enemy enhancement and botanical insecticide source: a review of dual use companion plants. Applied Entomology and Zoology 54(1): 1-19.

Badolo A et al., 2022. First comprehensive analysis of Aedes aegypti bionomics during an arbovirus outbreak in west Africa: Dengue in Ouagadougou, Burkina Faso, 2016–2017. PLoS Neglected Tropical Diseases 16(7): 0010059.

Bagiwa LS et al., 2022. Mosquito Vectors Associated with Lymphatic Filariasis in some Endemic Rural Communities of Katsina State, Nigeria. ATBU Journal of Science, Technology and Education 10(1): 360-366.

Balakumar M et al., 2022. Dengue outbreak and severity prediction: current methods and the future scope. Virus Disease 1-7.

Banjara MR et al., 2019. Integrating case detection of visceral leishmaniasis and other febrile illness with vector control in the post-elimination phase in Nepal. The American Journal of Tropical Medicine and Hygiene 100(1): 108.

Banks SD et al., 2014. Insecticide-treated clothes for the control of vector-borne diseases: a review on effectiveness and safety. Medical and Veterinary Entomology 28: 14-25.

Belmain SR et al., 2012. Highly variable insect control efficacy of Tephrosia vogelii chemotypes. Journal of Agricultural and Food Chemistry 60(40): 10055-10063.

Bian G et al., 2013. Wolbachia invades Anopheles stephensi populations and induces refractoriness to Plasmodium infection. Science 340(6133): 748-751.

Bohari R et al., 2020. Wide area spray of bacterial larvicide, Bacillus thuringiensis israelensis strain AM65-52, integrated in the national vector control program impacts dengue transmission in an urban township in Sibu district, Sarawak, Malaysia. PloS one 15(4): 0230910.

Boulogne I et al., 2012. Insecticidal and antifungal chemicals produced by plants: a review. Environmental Chemistry Letters 10(4): 325-347.

Bruhl CA et al., 2020. Environmental and socioeconomic effects of mosquito control in Europe using the biocide Bacillus thuringiensis subsp. israelensis (Bti). Science of the Total Environment 724: 137800.

Christian UA et al., 2021. Environmental Manipulation: A Potential Tool for Mosquito Vector Control. The Wonders of Diptera-Characteristics, Diversity and Significance for the World's Ecosystems.

Collins JP, 2018. Gene drives in our future: challenges of and opportunities for using a self-sustaining technology in pest and vector management. In *BMC* proceedings 12: 37-41).

De Las Llagas LA et al., 2016. Aedes dengue vector ovitrap surveillance system: a framework for mosquito density prediction. The Southeast Asian Journal of Tropical Medicine and Public Health 47(4): 712-718.

Dewar CE et al., 2022. Oxidative phosphorylation is required for powering motility and development of the sleeping sickness parasite Trypanosoma brucei in the tsetse fly vector. mBio 13(1): 02357-02321.

Dhiman RC and Yadav RS, 2016. Insecticide resistance in phlebotomine sandflies in Southeast Asia with emphasis on the Indian subcontinent. Infectious Diseases of Poverty 5(6): 1-10.

Dinesh DS et al., 2014. The potentiality of botanicals and their products as an alternative to chemical insecticides to sandflies (Diptera: Psychodidae): A review. Journal of Vector Borne Diseases 51(1): 1.

Doloi D, 2021. A study on certain biological control methods to control and manage vector-borne diseases. International Journal of Mosquito Research 8(1): 31-34.

Duchon S et al., 2014. Pyrethrum: a mixture of natural pyrethrins has potential for malaria vector control. Journal of Medical Entomology 46(3): 516-522.

Dulacha D, 2022. Reduction in malaria burden following the introduction of indoor residual spraying in areas protected by long-lasting insecticidal nets in Western Kenya, 2016–2018. Plos one 17(4): 0266736.

Ellse L et al., 2016. Essential oils in the management of the donkey louse, Bovicola ocellatus. Equine Veterinary Journal 48(3): 285-289.

Elnaiem DEA et al., 2020. Outdoor residual insecticide spraying (ODRS), a new approach for the control of the Exophilic vectors of human visceral Leishmaniasis: Phlebotomus Orientalis in East Africa. PLoS Neglected Tropical Diseases 14(10): 0008774.

Emami MM et al., 2009. Efficacy of Olyset long-lasting bednets to control transmission of cutaneous leishmaniasis in Iran. Eastern Mediterranean Health Journal 15(5): 1075-1083.

Faraj C et al., 2013. Field evaluation of alphacypermethrin in indoor residual spraying for leishmaniasis control in an endemic area, northern Morocco. Parasites and Vectors 6(1): 1-7.

Faulde MK, 2018. Long-lasting insecticide-treated textiles preventing from mosquito bite and mosquito-borne diseases. In: Mosquito-borne Diseases; pp: 281-303.

Ghosh SK and Dash AP, 2007. Larvivorous fish against malaria vectors: a new outlook. Transactions of the Royal Society of Tropical Medicine and Hygiene 101(11): 1063-1064.

Girma MB et al., 2021. Mechanism of Action of N-Acyl and N-Alkoxy Fosmidomycin Analogs: Mono-and Bisubstrate Inhibition of IspC from Plasmodium falciparum, a Causative Agent of Malaria. ACS Omega 6(42): 27630-27639.

Gnankine O and Bassole IHN, 2017. Essential oils as an alternative to pyrethroids' resistance against Anopheles species complex giles (Diptera: Culicidae). Molecules 22(10): 1321.

Grieco JP et al., 2007. A new classification system for the actions of IRS chemicals traditionally used for malaria control. PLos one 2(8): 716.

Gunay F et al., 2014. Evaluation of the efficacy of Olyset® Plus in a village-based cohort study in the Cukurova Plain, Turkey, in an area of hyperendemic cutaneous leishmaniasis. Journal of Vector Ecology 39(2): 395-405.

Huda MM et al., 2019. Intervention packages for early visceral leishmaniasis case detection and sandfly control in Bangladesh: A comparative analysis. The American Journal of Tropical Medicine and Hygiene 100(1): 97.

Halstead SB, 1978. Studies on the attenuation of dengue 4. Asian J Infect Dis 2: 112-117.

Isman MB, 2017. Bridging the gap: Moving botanical insecticides from the laboratory to the farm. Industrial Crops and Products 110: 10-14.

Isman MB, 2020. Botanical insecticides in the twenty-first century—fulfilling their promise? Annual Review of Entomology 65: 233-249.

James LD et al., 2022. Field trials reveal the complexities of deploying and evaluating the impacts of yeast-baited ovitraps on Aedes mosquito densities in Trinidad, West Indies. Scientific reports 12(1): 1-13.

Jung JY et al., 2021. Improved stability of CdSeS/ZnS quantum dots against temperature, humidity, and UV-O3 by encapsulation in crosslinked polystyrene beads. Journal of Materials Science 56(21): 12315-12325.

Kahamba NF et al., 2022. Using ecological observations to improve malaria control in areas where Anopheles funestus is the dominant vector. Malaria Journal 21(1): 1-15.

Kaindoa EW et al., 2021. Insecticide-treated eave ribbons for malaria vector control in low-income communities. Malaria Journal 20(1): 1-12.

Killeen GF et al., 2017. Control of malaria vector mosquitoes by insecticide-treated combinations of window screens and eave baffles. Emerging Infectious Diseases 23(5): 782.

Kirby MJ et al., 2009. Effect of two different house screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial. The Lancet 374(9694): 998-1009.

Krivosheina EI et al., 2021. Advanced Laboratory Methods for Detecting Yellow Fever Pathogen. Problemy Osobo Opasnykh.

Lee JK et al., 2018. Transmission of Amblyomma maculatum-associated Rickettsia spp. during cofeeding on cattle. Vector-Borne and Zoonotic Diseases 18(10): 511-518.

Lindblade KA et al., 2015. A cohort study of the effectiveness of insecticide-treated bed nets to prevent malaria in an area of moderate pyrethroid resistance, Malawi. Malaria Journal 14(1): 1-15.

Lindsay SW et al., 2021. Recommendations for building out mosquito-transmitted diseases in sub-Saharan Africa: the DELIVER mnemonic. Philosophical Transactions of the Royal Society B 376(1818): 20190814.

Lindsay SW et al., 2021. Threats to the effectiveness of insecticide-treated bednets for malaria control: thinking beyond insecticide resistance. The Lancet Global Health 9(9): 1325-1331.

Linn SY et al., 2019. Barriers in distribution, ownership and utilization of insecticide-treated mosquito nets among migrant population in Myanmar, 2016: a mixed methods study. Malaria Journal 18(1): 1-16.

Lupenza ET et al., 2021. Using pastoralist community knowledge to locate and treat dry-season mosquito breeding habitats with pyriproxyfen to control Anopheles gambiae sl and Anopheles funestus sl in rural Tanzania. Parasitology Research 120(4): 1193-1202.

Madgwick PG and Kanitz R, 2022. Modelling new insecticide-treated bed nets for malaria-vector control: how to strategically manage resistance? Malaria Journal 21(1): 1-20.

Malaria RB, 2015. Housing and malaria consensus statement. Vector Control Working Group. New York: Roll Back Malaria Partnership.

Matthews G, 2022. Can Malaria Be Eradicated by 2030? Outlooks on Pest Management 33(2): 76-77.

Messenger LA and Rowland M, 2017. Insecticide-treated durable wall lining (ITWL): future prospects for control of malaria and other vector-borne diseases. Malaria Journal 16(1): 1-18.

Mitchell C et al., 2020. Protective effectiveness of long-lasting permethrin impregnated clothing against tick bites in an endemic Lyme disease setting: a randomized control trial among outdoor workers. Journal of Medical Entomology 57(5): 1532-1538.

Manning JE and Cantaert T, 2019. Time to micromanage the pathogen-host-vector interface: considerations for vaccine development. Vaccines 7(1): 10.

Moyes CL et al., 2017. Contemporary status of insecticide resistance in the major Aedes vectors of arboviruses infecting humans. PLoS Neglected Tropical Diseases 11(7): 0005625.

Msugupakulya BJ et al., 2020. Preferred resting surfaces of dominant malaria vectors inside different house types in rural south-eastern Tanzania. Malaria Journal 19(1): 1-15.

Newby G et al., 2021. Global health security requires endemic disease eradication. The Lancet 397(10280): 1163-1165.

Nuttall, PA, 1999. Pathogen-tick-host interactions: Borrelia burgdorferi and TBE virus. Zentralblatt für Bakteriologie 289(5-7): 492-505.

Odintsova O and Lipina A, 2022. Promising Preparations for Acaricide Repellent finishing of textile materials. From Chemistry towards technology step-by-step 3(1): 123-130.

Pavela R et al., 2019. Plant extracts for developing mosquito larvicides: From laboratory to the field, with insights on the modes of action. Acta Tropica 193: 236-271.

Picado A et al., 2010. Effect of village-wide use of long-lasting insecticidal nets on visceral Leishmaniasis vectors in India and Nepal: a cluster randomized trial. PLoS Neglected Tropical Diseases 4(1): 587.

Pugliese M et al., 2021. Natural Products against Sand Fly Vectors of Leishmaniosis: A Systematic Review. Veterinary Sciences 8(8): 150.

Ramzan M et al., 2021. Techniques for managing ticks and tick-borne diseases under changing climate; A review. Egyptian Academic Journal of Biological Sciences, B. Zoology 13(1): 117-128.

Remme, JHF et al., 2021. Tropical diseases targeted for elimination: Chagas disease, lymphatic filariasis, onchocerciasis, and leprosy. International Journal of Biomedical and Health Sciences. 9(4)

Richards SL et al., 2018. Permethrin treated clothing to protect outdoor workers: evaluation of different methods for mosquito exposure against populations with differing resistance status. Pathogens and Global Health 112(1): 13-21.

Ritchie SA and Devine GJ, 2013. Confusion, knock-down and kill of Aedes aegypti using metofluthrin in domestic settings: a powerful tool to prevent dengue transmission? Parasites and Vectors 6(1): 1-9.

Ritchie SA et al., 2021. Insecticide-based approaches for dengue vector control, Ecology and Control of Vector-borne Diseases. Wageningen Academic Publishers, Wageningen, Netherlands.

Ruiz-Castillo P, 2021. Insecticide-Treated livestock: A potential One Health approach to malaria control in Africa. Trends in Parasitology.

Saghafipour A et al., 2016. Bioassay evaluation of residual activity of attractive toxic sugar-treated barrier fence in the control of Phlebotomus papatasi (Diptera: Psychodidae). Journal of Vector Borne Diseases 53(4): 335.

Saghafipour A et al., 2017. Control of zoonotic cutaneous leishmaniasis vector, Phlebotomus papatasi, using attractive toxic sugar baits (ATSB). PLoS One 12(4): 0173558.

Samanmali C et al., 2018. Larvicidal potential of five selected dragonfly nymphs in Sri Lanka over Aedes aegypti (Linnaeus) larvae under laboratory settings. BioMed Research International 1-10.

Shan J et al., 2021. Targeting multicopy prophage genes for the increased detection of Borrelia burgdorferi sensu lato (sl), the causative agents of Lyme disease, in blood. Frontiers in microbiology 12: 651217.

Shaw WR et al., 2016. Wolbachia infections in natural Anopheles populations affect egg laying and negatively correlate with Plasmodium development. Nature Communications 7(1): 1-7.

Shin A et al., 2022. Tick-borne encephalitis virus and West-Nile fever virus as causes of serous meningitis of unknown origin in Kazakhstan. Zoonoses and Public Health.

Singh H et al., 2022. Sustainable control of malaria employing Gambusia fishes as biological control in Jalore and Barmer districts of Western Rajasthan. Journal of Vector Borne Diseases 59(1): 91.

Schuerman L, 2019. RTS, S malaria vaccine could provide major public healt benefits. The Lancet 394: 735-736.

Singh OP et al., 2021. Xenodiagnosis to evaluate the infectiousness of humans to sandflies in an area endemic for visceral leishmaniasis in Bihar, India: a transmission-dynamics study. The Lancet Microbe 2(1): 23-31.

Sormunen JJ et al., 2021. Absence of Francisella tularensis in Finnish Ixodes ricinus and Ixodes persulcatus ticks. Ticks and Tick-borne Diseases 12(6): 101809.

Sridhar S et al., 2018. Effect of dengue serostatus on dengue vaccine safety and efficacy. New England Journal of Medicine 379(4): 327-340.

Sternberg ED et al., 2021. Impact and cost-effectiveness of a lethal house lure against malaria transmission in central Côte d'Ivoire: a two-arm, cluster-randomised controlled trial. The Lancet 397(10276): 805-815.

Tembo Y et al., 2018. Pesticidal plant extracts improve yield and reduce insect pests on legume crops without harming beneficial arthropods. Frontiers in Plant Science 9: 1425.

Thizy D et al., 2019. Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods. PLoS Neglected Tropical Diseases 13(4): 0007286.

Tisgratog R et al., 2016. Plants traditionally used as mosquito repellents and the implication for their use in vector control. Acta Tropica 157: 136-144.

Tyagi BK, 2016. Advances in vector mosquito control technologies, with particular reference to herbal products. In: Veer V, Reji G, editors. Herbal insecticides, repellents and biomedicines: effectiveness and commercialization. Springer: New Delhi; pp: 1-9.

Van den Berg H et al., 2021. Management of insecticides for use in disease vector control: Lessons from six countries in Asia and the Middle East. PLoS Neglected Tropical Diseases 15(4): 0009358.

Vang A et al., 2022. Evaluation of surface versus total permethrin content in permethrin-treated clothing: Implications for protection against mosquitoes. Pathogens and Global Health 1-11.

Venkatesh A and Tyagi BK, 2013. Predatory potential of Bradinopyga geminata and Ceriagrion coromandelianum larvae on dengue vector Aedes aegypti under controlled conditions (Anisoptera: Libellulidae; Zygoptera: Coenagrionidae; Diptera: Culicidae). Odonatologica 42(2): 139-149.

Viana JL et al., 2021. Larvicide activity of Bacillus thuringiensis var. israelensis. in simulated field condition. Brazilian Journal of Development 7(4): 43248-43264.

Wilke ABB and Marrelli MT, 2015. Paratransgenesis: a promising new strategy for mosquito vector control. Parasites and vectors 8(1): 1-9.

Wilson AL et al., 2020. The importance of vector control for the control and elimination of vector-borne diseases. PLoS Neglected Tropical Diseases 14(1): 0007831.

World Health Organization, 2012. World Malaria Report 2012, World Health Organization.

World Health Organization, 2015. Global technical strategy for malaria 2016-2030. http://www.who.int/malaria/publications/atoz/9789241564991/en/

World Health Organization 2017. Global vector control response. Global vector control response 2017-2030.

World Health Organization, 2020. Vector-borne diseases (fact sheet). https://www.who.int/news-room/factsheets/detail/vector-borne-diseases (Accessed June 22, 2021).

World Health Organization, 2018. Revised SAGE recommendation on use of dengue vaccine. [Cited 23 Aug 2019].

Xiang R et al., 2022. Research history and progress of six vector chigger species of scrub typhus in China. Systematic and Applied Acarology 27(9): 1841-1856.

Yamaoka Y et al., 2021. Zika virus protease induces caspase-independent pyroptotic cell death by directly cleaving gasdermin D. Biochemical and Biophysical Research Communications 534: 666-671

26

Detection of Emerging Zoonotic Pathogens: An Integrated One Health Approach

AUTHORS DETAIL

Momna Mehmood*, Muhammad Naeem Faisal, Muhammad Abdullah, Aiza Kamal Khan, Wania Nasir, Usman Haider, Najeeb Ullah Khan and Aneela Gul

University of Agriculture Faisalabad, Pakistan
*Corresponding author: m.naeem.faisal@uaf.edu.pk

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INTRODUCTION

Now a day the management of human health is all about finding and combating new challenges imposed by emerging pathogenic as well as opportunistic microorganisms with major global concerns. Such emerging diseases are crossing the borders and transferring throughout the world in almost every kind of environment. A major concern gathering the attention of healthcare system worldwide is the transmission of many diseases from animals to humans via zoonosis (Rahman et al. 2020). Such zoonotic diseases can emerge because of intermittent disease outbreaks or new epidemic diseases. Such animals are the main cause of spreading various diseases in humans as well. The opportunistic pathogens can get an entry from animal host to human host through two ways, either interacting directly via zoonoses or by using some vectors, ultimately disturbing human health. Such interaction between humans and animals affecting the health of both comes under the umbrella of "one health". The concept of One health links all three components i.e., animal, human and environment health, together (Bird and Mazet 2018).

Therefore, understanding and working on one health approach is much important in controlling the new emerging zoonotic diseases. By applying the one health approach for zoonotic disease management we may consider the involvement of multiple disciplines, such as mammologists, entomologists, ornithologists, ecologists, physicians and epidemiologists for successful investigations and diagnostics (Humboldt-Dachroeden et al. 2020). In this chapter, we will seek to review and explain the various diagnostic methods for the detection of newly infecting agents. Different affective approaches will also be discussed to improve the disease surveillance programs by engaging the local community for the rapid discovery of new threats to human as well as animal health.

The Emerging Zoonoses Pathogen Context

According to an emerging disease hypothesis, pathogenic determinants breeding is considered in evolved disease patterns by utilizing any possible convenient biological host. One of the most commonly available biological host for resistant pathogenic determinants breeding, is animal. Almost 50% of the pathogens causing diseases in humans originate from animals which is the reason for more zoonotic threats to humans as compared to other diseases (Daszak et al. 2000; Cleaveland et al. 2001; Woolhouse and Gaunt 2007; Jones et al. 2008). According to 17th US-National Institutes of Health, almost all pathogens of Category A are zoonotic in nature which can cause severe human illnesses (Woolhouse and Gowtage-Sequeria 2005). However, these pathogens having zoonotic nature are only a minor fraction of total existing pathogenic organisms (Bebber et al. 2007; Anthony et al. 2013). The remaining unknown pathogens yet to discover, pose the need for a sustainable detection networks under the principles of one-health to prevent any pandemic situation in the world (Grange et al. 2021).

Along with biological factors, there is also a strong influence imposed by the sociology, ecology and behavioral reactions of animals and humans in the transmission of newly emerging infectious agents from animal hosts to the first human host which can result in the great dissemination as well as transmission in the human population at mass level (Wolfe et al. 2007; Morse et al. 2012; Kreuder Johnson et al. 2015).

There is an intense need for the robust and broad-based detection systems for the emerging zoonotic pathogens i.e., Ebola virus (Zaire ebolavirus), as being a relatively well-known pathogen, exposed in 2013 in Liberia, can be taken as an example for such needs (Baize et al. 2014; Dixon and Schafer 2014; Dudas et al. 2017). Of the fact that disease by Ebola virus has come into recognition from over forty years, this outbreak intensified rapidly with sixty times higher case rate as compared to the previous outbreak of Ebola (WHO 1978). An approximate increase of 11000 casualties was reported in a time of three years. Also, the virus was emerged in seven more countries where it affected individuals severely. It was reported that improved pathogen detection and disease control programs being stretched to local as well as international levels helped in the timely recognition and diagnosis of the virus (Bell 2016; Coltart et al. 2017).

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Although there was a tremendous increase in advancement in diagnostic methodologies since 1976, there is still a need for preparation of integrated and resilient laboratories along with efficient surveillance systems for both human and animal diseases. Hence, rapid identification of potential health risks via technical expertise is need of the hour. All this requires a sustainable and consistent funding, technical training sessions and involvement of partners from all over the world (Kuleš et al. 2017).

Biology and Behavior: An Interface Between Animals, Humans and Pathogens

There has always been a strong relationship between humans and animals since the beginning. Along with several benefits gained by animals, such as food, companionship, and fiber there is also a change in lifestyles, behaviors and food choices which can influence the dynamics of zoonotic disease emergence (Lloyd-Smith et al. 2009). Increasing human population has increased the demand for wild and domesticated animal products. Such increased demands result in need for land to grow animals and their feedstuffs. This whole condition can lead to the expansion of animal's production system in wildlife abundant areas resulting in high-consequence zoonotic disease emergence such as henipa viruses, Crimean-Congo hemorrhagic fever virus, Middle East respiratory syndrome-coronavirus, tick-borne bunyaviruses, thrombocytopenia syndrome virus, monkeypox and ebolaviruses (Croser and Marsh 2013; Liu et al. 2014; de Wit et al. 2016). However, direct contact of humans and wildlife for their meat consumption, hunting and slaughtering remains a key driver of above mentioned zoonoses emergence (Robertson et al. 2011; Engering et al. 2013; Suwannarong and Schuler 2016). There exists a continuous close interaction and affiliation between animals, humans, and pathogenic organisms all around the world which increases the risk for the emergence of pandemic diseases. Such pandemic conditions can threaten the lives of many humans and animals (Karesh et al. 2012; Morse et al. 2012; Morens and Fauci 2013). To overcome these challenges related to zoonotic disease exposure in future, intensive and early engagement of the community by disease diagnosis and surveillance professionals and medical anthropologists becomes imperative so that to make such leaders a part of various comprehensive and integrated disease surveillance system for zoonotic diseases (Richardson et al. 2016; Shultz et al. 2016).

The Emerging Pathogen-detection Pathway

The initial pathogen detection of zoonotic threats may begin at local levels. One can start the detection methods by simply observing the sick individuals either humans or animals for the signs and symptoms of the disease. Assistance can be taken by someone who is familiar to the common diseases and their signs, prevailing in the specific area. Such initial observation never gets reported at mass level however, some cases can lead to the involvement of local, national, and international agencies at government level. Centralized systems are developed in many countries for epidemiological as well as laboratory techniques of disease diagnosis at national level diagnostic centers which are basically distant from main area of disease emergence with a high risk of human to animal interaction (Alemnji et al. 2014). In such instances, clinical information of patient/animal, mortality number and diagnostic samples of patients and dead persons for clinical testing are transferred from local areas to such referral centers at national and international levels. Instead of several successes, failure of this centralized system can occur due to issues including poor communication and transportation facilities, less no. of trained workers and suboptimal reporting systems at national levels, which can all add up in delaying the process of recognition, disease diagnosis and emerging disease risk control (Best and Sakande 2016).

Building Effective Surveillance Networks

The main goal of any disease surveillance system should be an early, rapid, and easy detection of emerging threats by integrating the animal and human health sectors as close as possible. To achieve such goals both animal and human health workers as well as ecology testing teams of field level who are working for common scientific and health goals of common public would work together for detecting newly emerging zoonotic pathogens of animal and human population. Such integrated approaches may work ideally at local levels as compared to the centralized systems, by using the local technical training along with diagnostic laboratory systems for zoonotic ailment's detection (Bird and Mazet 2018). Although it may become difficult to handle the distributed diagnostic systems at local levels in terms of expenses and training of staff, but by choosing a closely established and highly integrated detection system at local community level, it may result in rapid detection and a smoother and easy follow up of rare health events (Land et al., 2019).

The need of the hour is to build the effective surveillance networks at local as well as regional levels under the utilization of sustainable funds, infrastructure, and lab technologies in an integrated way. In wake of pandemic situation by SARS in 2001, International Health Regulations (IHR) were adopted in 2005 by 196 countries who were member of World Health Organization (WHO). Therefore, regulations like IHR have cleared the idea of spread of diseases from animals to humans or humans to animals through movement which emphasizes the need to link human and the animal's surveillance systems closely (WHO 2016).

Many funding agencies such as World health organization (WHO), world bank, USAID, UN Food and Agriculture

Organization and government services can collaborate to augment the surveillance programs and manage the training burdens for facilitating the rapid and robust training sessions to enhance the disease surveillance and diagnostic capacities. Such hands-on personnel trainings are much necessary for developing one-health surveillance team. Trainings for surveillance programs vary country to country such as the PREDICT program engages many countries including highly advanced ones with proper medical care centers to the countries with lowest possible facilities in terms of basic infrastructure and number of trained staff to span the disease diagnosis spectrum.

Predict

A project, named PREDICT was initiated for USAID Emerging Pandemic Threats Program, in 2009. The main concern was to address the need of strengthening the capacity of pathogen discovery and detection methods for viruses having pandemic potential along with their zoonotic importance. Some most important zoonotic diseases caused by highly contagious viruses include corona virus, Nipah virus, filoviruses as Ebola virus and influenza viruses. These pathogens were highly focused in second 5-year phase of this PREDICT project. PREDICT is working with thirty countries and sixty in-country laboratories. The main purpose is to improve disease recognition and to minimize the pandemic risks by focused strategy making policy development under one health approach at global level (Carlson 2020). The main goal of this project is to identify the infectious agents of zoonotic importance at an early stage of disease spread so that the pandemic situation could be avoided. For that purpose, surveillance systems and pathogen diagnostic laboratories are being improved for their diagnostic capabilities, especially by using modern diagnostic techniques such as PCR (Anthony et al. 2015). The leader institutes of the project are trying to build some one health partnership at global level. Such cross disciplinary collaboration is critically important for the integral linkage between humans, animals and their environment for timely detection and control of zoonotic threats (Kelly et al. 2020).

The Tanzania VISHA (VIRUS-SHARING) Project

The Tanzania VISHA virus sharing is another collaborated model One-Health project of one health institute by The Sokoine University of Agriculture in Morogoro, Tanzania and The University of California, Davis. The purpose was to focus on enhancement of capacity building for increasing disease detection systems within the country to ultimately improve the health status of animals and the people coming in contact with the animals. Recently, this collaborated project has been referred as Healthy Animals and Livelihood Improvement (HALI). Many improvements are made with reference to the disease surveillance programs, trained laboratory staffs and lab detection protocols for zoonotic diseases under intense consideration of environmental and ecological influence on pathogen and population dynamics (Mazet et al. 2009).

Laboratory Testing System Integration

Over the past 40 years, there has been a tremendous advancement in the quality and variety of sample collection and the diagnostic technologies (Sridhar et al. 2015). Such vast evolution in the field of diagnostics and the use of modern technologies has led to a comprehensive understanding of emerging microbes and their potential zoonoses. Diagnostic laboratories are being equipped with all the required materials and technically trained staff. Diseases are being detected both for their acute and convalescent phases (Bird et al. 2009; Erickson et al. 2016).

Disease Diagnostic Methods

A lot of revolution has been made in the field of pathogen discovery methods. Many highly specific and sensitive molecular techniques have been discovered such as NAAT technologies including PCR for DNA amplification and RT-PCR using reverse transcriptase enzyme for RNA amplification. Such techniques based on the principle of direct detection of pathogen’s genome. Other NAAT techniques having real-time quantitative PCR, consensus PCR and Sanger whole-genome sequencing have played a great role in changing the diagnostic spectrum such as for viral pathogens (Zumla et al. 2014). However, a limitation while using these techniques is the low knowledge about the new emerging pathogen’s genome or variations in the new strains of the pathogens. Strategies are being made to overcome such limitations by developing further modern detection protocols and methods i.e., high-throughput sequencing or unbiased next-generation sequencing (NGS) (Radford and Bushell 2012; Radford et al. 2012; Chiu 2013; Moustafa et al. 2017). Traditional PCR techniques are also being refined as per strategies for using intensely degenerate primers for detection and amplification of genomic material across the pathogenic viral families (Linhart and Shamir 2005; Souvenir et al. 2007).

Conventional Methods for Zoonotic Disease Diagnosis

Conventional methods for zoonotic disease diagnosis can be categorized as macroscopic and microscopic pathogen identification by using different stains for morphological identification of disease-causing agents under microscope. Staining procedures include gram stain, immuno fluorescent stain and fluorochrome stain helping in narrow organism identification (Bunn and Sikarwar 2016).

Microscopic Analysis

Disease diagnosis initiates with direct and indirect demonstration of pathogenic organisms such as viruses, bacteria, fungi, and parasites in the samples of fluids, tissues, and host excreta (Bunn and Sikarwar 2016; Schwarz et al. 2017). Microscopic analysis, staining and microbial growth are serving for pathogen detection since ages (Rodrigues et al. 2010). In such techniques, phenotypic characters play most important role in pathogen detection. Such characters may include cytopathic effects in tissue cultures for detecting viral agents, bacterial fermentation profiles and fungal and parasitic morphology under the microscope. One limitation of these techniques is the time consumption. All of these procedures are time consuming and may take more time to identify the pathogenic agent that's why genome-based analysis is more common in laboratories.

Phenotypic Methods

Phenotypic methods help in discriminating between species, genera and isolates of pathogenic organisms. However, these tests are not so effective when distinguishing the differences within species. The recently emerged pathogens and the bioterrorist agents have made it much necessary for the development of new, rapid, and efficient methods for pathogen detection (Gilbert 2002).

Pathogen Isolation and Culture

Another conventional technique for pathogen detection is the isolation and culturing. Pathogenic agents including SARS-CoV, Sosuga virus, Ebola virus and Nipah virus can be isolated and analyzed by this method. It is a sensitive technique in which pathogen remains available for further analysis and is also useful for detection of unknown pathogens. However, the choice of media or cell line may limit the level of sensitivity as well as detection for unknown samples (Paton et al. 1999; Ksiazek et al. 2003; Albarino et al. 2014). Manual reading of plates by staff is a lengthy process and take much time which also interrupts the normal flow of biochemical analysis thus extending the whole procedure (Eydmann 2011).

Rapid Diagnostic Tests or Lateral Flow Assays

Rapid tests like plate agglutination tests are also being used which need no electricity, low operating skills and are thermostable. However, sensitivity is limited and can't interpret weak results. It is also not suitable for the discovery of unknown pathogens. Viruses like Influenza virus and Ebola virus can easily be detected by using this technique (Cazacu et al. 2003; Phan et al. 2016).

Conventional PCR/RT-PCR and Sequencing

One of the most common techniques that involve genome sequencing methods is PCR. It is highly sensitive and specific technique depending on the design of primer. It can broadly react and PCR amplicons are usually sequenced for detailed confirmation and characterization of the pathogen. Limitations include moderate requirements for technical and lab work (Towner et al. 2008). Also, the reagents being used in PCR require the maintenance of cold chain. Contamination may occur easily so high germ-free environment is required while dealing with the method otherwise inaccurate and difficult interpretation of the results may happen. Some examples of the pathogens being detected by this method are Bundibugyo virus, Sin Nombre virus, MERS-like CoV, Ngari virus and coronaviruses (Bowen et al. 2001; Anthony et al. 2017).

Modern Methods for Zoonotic Disease Diagnosis

When the pathogen can't grow outside the host environment and can't be detected by simple methods like microscopic analysis then some modern methods are used for diagnostic purposes. Such methods include a sensitive and specific molecular diagnosis of the pathogen (Nissen and Sloots 2002; Leland and Ginocchio 2007).

Electron Microscopy

This is a type of modern microscopic method using electron microscope. It is being used for in situ Visualization of the pathogenic organism. High technical expertise is required for slide preparation and running of microscope. Examples of pathogens being detected include SARS-CoV and expensive Ebola virus (Ksiazek et al. 2003).

Histology/Immunohistochemistry

Immunohistochemistry is being used for analyzing tissue pathology. This technique works on the antigen-antibody reaction principle, and requires cross reactive antisera. Highly technical expertise are needed for pathogen detection. Viruses like Zika virus in CNS tissue of neonates is being detected by this method (Martines 2016).

Antigen Capture and IgM ELISA

ELISA is being used to capture the antigen and it is based on antigen-antibody principle. Specifically, IgM ELISA is being used for multiple commercial as well as experimental purposes. It is adapted with high-throughput screening and proves to be excellent counterpart for molecular analysis of unknown pathogens during a newly emerged outbreak. Limitations include the requirement of cross-reactive antisera. Some samples may also have sticky serum which can result in false positive reports (Towner et al. 2008; Broadhurst et al. 2016).

IgG ELISA Techniques

IgG ELISA is being used for the broad detection of infections which have been occurred in the past. Multiple experimental and commercial assays are analyzed by this method. Highly specific and cross-reactive antibody titers are being used for such analysis. It serves as the primary tool for the serosurveys postexposure to the infection. IgG ELISA requires specific antigen and antisera. Cross reactivity with antibody may confound the results (Hernández-González et al. 2018).

Phage Display Antibody Detection

Phage display method has a great potential for wide range detection of antibodies of diverse pathogens. However, it is an expensive and high demanding technique being used for experimental purposes (Xu et al. 2015).

Whole Genome Sequencing

Whole genome sequencing techniques include NGS or HTS being used for unbiased genome detection specially for unknown pathogens. Risk assessment is also possible by this method (Al Dahouk et al. 2013). NGS techniques are being used for tracking of virus dispersal i.e., ongoing transmissions versus reintroduction in a population. Limitations include need of highly expert lab staff specially for bioinformatics, low sensitivity, and high cost of the procedure. List of pathogens being detected include Heartland virus, Bas-Congo virus, Sosuga virus and SFTS virus (Xu et al. 2011; Yu et al. 2011; Grard et al. 2012; McMullan et al. 2012).

Quantitative Real-time PCR/RT-PCR

QRT PCR is a highly sensitive and specific method. It is an example of NAAT (Nucleic Acid Amplification Test) technology being used for rapid test of organisms like methicillin resistant *Staphylococcus aureus* (MRSA) colonization in the nasal sinuses. Mostly it is being used for known pathogens. Another example includes Marburg virus detection in bat reservoir. Use of RT-PCR technique neglects the need of traditional detection and subculture of suspected isolates being present in normal flora (Stephanie et al. 2001). Recently innovations are made to ease the use of such quick methods up to the limit of a single click and the result is generated automatically. Chances for lab contamination, false positive and false negative results are also less in these methods. There are some limitations to use this technique which include less pathogen discovery for unknown agents and PCR amplicons may not be suitable for detection and genome sequencing (Towner et al. 2008).

Conclusion

Although there is a huge advent in the field of diagnostics in the past few years, for the timely detection of disease-causing organisms, however, need for robust system development for rapid detection of emerging zoonotic pathogens remains a massive challenge. Establishment of sustainable, long term diagnostic methods at both local as well as national levels remains a key step in identification and alert to public health organizations to avoid any approaching pandemic condition and zoonotic threats. We must need to be well prepared for recognizing the prevailing threats and to work in collaboration to avoid the infection spread and consequent health issues for both animals and humans present globally. For optimal use of diagnostic methods, sensitivity, specificity, cost effectiveness and availability of relevant staff to deal with specific methods must be considered before deciding a diagnostic method for a specific infectious agent. Now a days, diagnostic techniques involving manipulation with nucleic acid of pathogenic organisms are being used and become a center to all future approaches to health care system. A continues improvement in all mentioned techniques is ever needed. In this context, nanotechnology stands as a promising approach that provides new direction to the scientific community for developing much simplified assays with advanced detection capabilities. Such methods will play a promising role in designing the detection systems in coming future.

REFERENCES

Al Dahouk S et al., 2013. New developments in the diagnostic procedures for zoonotic brucellosis in humans. Review Science Technology 32(1): 177-188.

Albariño CG et al., 2014. Novel paramyxovirus associated with severe acute febrile disease, South Sudan and Uganda, 2012. Emerging Infectious Diseases 20(2): 211.

Alemnji GA et al., 2014. Strengthening national health laboratories in sub-Saharan Africa: a decade of remarkable progress. Tropical Medicine and International Health 19(4): 450-458.

Anthony SJ et al., 2013. A strategy to estimate unknown viral diversity in mammals. MBio 4(5): 00598-13.

Anthony SJ et al., 2015. Non-random patterns in viral diversity. Nature Communications 6(1): 8147.

Anthony SJ et al., 2017. Further evidence for bats as the evolutionary source of Middle East respiratory syndrome coronavirus. MBio 8(2): 00373-17.

Baize S et al., 2014. Emergence of Zaire Ebola virus disease in Guinea. New England Journal of Medicine 371(15): 1418-1425.

Bebber DP et al., 2007. Predicting unknown species numbers using discovery curves. Proceedings of the Royal Society B: Biological Sciences 274(1618): 1651-1658.

Bell BP 2016. Overview, control strategies, and lessons learned in the CDC response to the 2014–2016 Ebola epidemic. The Morbidity and Mortality Weekly Report Supplements 5: 65.

Best M and Sakande J, 2016. Practical recommendations for strengthening national and regional laboratory networks in Africa in the Global Health Security era. African Journal of Laboratory Medicine 5(3): 1-10.

Bird BH et al., 2009. Rift Valley fever virus. Journal of the American Veterinary Medical Association 234(7): 883-893.

Bird BH and Mazet JA 2018. Detection of emerging zoonotic pathogens: an integrated one health approach. Annual Review of Animal Biosciences 6: 121-139.

Bowen MD et al., 2001. A reassortant bunyavirus isolated from acute hemorrhagic fever cases in Kenya and Somalia. Virology 291(2): 185-190.

Broadhurst MJ et al., 2016. Diagnosis of Ebola virus disease: past, present, and future. Clinical Microbiology Reviews 29(4): 773-793.

Bunn TW and Sikarwar AS, 2016. Diagnostics: conventional versus modern methods. Journal of Advances in Medical and Pharmaceutical Sciences 8(4): 1-7.

Carlson CJ, 2020. From PREDICT to prevention, one pandemic later. The Lancet Microbe 1: 6-7.

Cazacu AC et al., 2003. Comparison of lateral-flow immunoassay and enzyme immunoassay with viral culture for rapid detection of influenza virus in nasal wash specimens from children. Journal of Clinical Microbiology 41(5): 2132-2134.

Chiu CY, 2013. Viral pathogen discovery. Current Opinion in Microbiology 16: 468-478.

Cleaveland S et al., 2001. Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 356(1411): 991-999.

Coltart CE et al., 2017. The Ebola outbreak, 2013–2016: old lessons for new epidemics. Philosophical Transactions of the Royal Society B: Biological Sciences 372(1721): 20160297.

Croser EL and Marsh GA, 2013. The changing face of the henipaviruses. Veterinary Microbiology 167(1-2): 151-158.

Daszak P et al., 2000. Emerging infectious diseases of wildlife--threats to biodiversity and human health. Science 287(5452): 443-449.

De Wit E et al., 2016. SARS and MERS: recent insights into emerging coronaviruses. Nature Reviews Microbiology 14(8): 523-534.

Dixon MG and Schafer IJ, 2014. Ebola viral disease outbreak—West Africa, 2014. Morbidity and Mortality Weekly Report 63(25): 548.

Dudas G et al., 2017. Virus genomes reveal factors that spread and sustained the Ebola epidemic. Nature 544(7650): 309-315.

Engering A et al., 2013. Pathogen–host–environment interplay and disease emergence. Emerging Microbes and Infections 2(1): 1-7.

Erickson BR et al., 2016. Ebola virus disease diagnostics, Sierra Leone: Analysis of real-time reverse transcription–polymerase chain reaction values for clinical blood and oral swab specimens. The Journal of Infectious Diseases 214: 258-262.

Eydmann M, 2011. Introduction of MALDI-TOF MS: A revolution in diagnostic microbiology. Biomedical Scientist 55(5): 329.

Gilbert GL, 2002. Molecular diagnostics in infectious diseases and public health microbiology: cottage industry to postgenomics. Trends in Molecular Medicine 8: 280-287.

Grange ZL et al., 2021. Ranking the risk of animal-to-human spillover for newly discovered viruses. Proceedings of the National Academy of Sciences 118(15): 2002324118.

Grard G et al., 2012. A novel rhabdovirus associated with acute hemorrhagic Fever in Central Africa 8: 1002924.

Hernández-González A et al., 2018. Evaluation of the recombinant antigens B2t and 2B2t, compared with hydatid fluid, in IgG-ELISA and immunostrips for the diagnosis and follow up of CE patients. PLoS Neglected Tropical Diseases 12(9): 0006741.

Humboldt-Dachroeden S et al., 2020. The state of One Health research across disciplines and sectors–a bibliometric analysis. One Health 10: 100146.

Jones KE et al., 2008. Global trends in emerging infectious diseases. Nature 451(7181): 990-993.

Karesh WB et al., 2012. Ecology of zoonoses: natural and unnatural histories. The Lancet 380(9857): 1936-1945.

Kelly TR et al., 2020. Implementing One Health approaches to confront emerging and re-emerging zoonotic disease threats: lessons from PREDICT. One Health Outlook 2: 1-7.

Kuleš J et al., 2017. The challenges and advances in diagnosis of vector-borne diseases: where do we stand? Vector-Borne and Zoonotic Diseases 17(5): 285-296.

Kreuder Johnson C et al., 2015. Spillover and pandemic properties of zoonotic viruses with high host plasticity. Scientific Reports 5(1): 1-8.

Ksiazek TG et al., 2003. A novel coronavirus associated with severe acute respiratory syndrome. New England Journal of Medicine 348: 1953-1966.

Land KJ et al., 2019. REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. Nature Microbiology 4(1): 46-54.

Leland DS and Ginocchio CC, 2007. Role of cell culture for virus detection in the age of technology. Clinical Microbiology Reviews 20(1): 49-78.

Linhart C and Shamir R, 2005. The degenerate primer design problem: theory and applications. Journal of Computational Biology 12(4): 431-456.

Liu Q et al., 2014. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. The Lancet Infectious Diseases 14(8): 763-772.

Lloyd-Smith JO et al., 2009. Epidemic dynamics at the human-animal interface. Science 326(5958): 1362-1367.

Martines RB, 2016. Notes from the field: evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses—Brazil, 2015. Morbidity and mortality weekly report 65.

Mazet JA et al., 2009. A "one health" approach to address emerging zoonoses: the HALI project in Tanzania. PLoS Medicine 6(12): 1000190.

McMullan LK et al., 2012. A new phlebovirus associated with severe febrile illness in Missouri. New England Journal of Medicine 367(9): 834-841.

Morens DM and Fauci AS, 2013. Emerging infectious diseases: threats to human health and global stability. PLoS Pathogens 9: 1003467.

Morse SS et al., 2012. Prediction and prevention of the next pandemic zoonosis. The Lancet 380(9857): 1956-1965.

Moustafa A et al., 2017. The blood DNA virome in 8,000 humans. PLoS Pathogens 13(3): 1006292.

Nissen MD and Sloots TP, 2002. Rapid diagnosis in pediatric infectious diseases: the past, the present and the future. The Pediatric Infectious Disease Journal 21(6): 605-612.

Towner JS et al., 2008. Newly discovered ebola virus associated with hemorrhagic fever outbreak in Uganda. PLoS Pathogens 4(11): 1000212.

Paton NI et al., 1999. Outbreak of Nipah-virus infection among abattoir workers in Singapore. The Lancet 354(9186): 1253-1256.

Phan JC et al., 2016. Lateral flow immunoassays for Ebola virus disease detection in Liberia. The Journal of Infectious Diseases 214: 222-228.

Radford A and Bushell C, 2012. How new sequencing technologies will help shape the future. The Veterinary Record 170(18): 471.

Radford AD et al., 2012. Application of next-generation sequencing technologies in virology. The Journal of General Virology 93: 1853.

Rahman M et al., 2020. Zoonotic diseases: etiology, impact and control. Microorganisms 8(9): 1405.

Richardson ET et al., 2016. Biosocial approaches to the 2013-2016 Ebola pandemic. Health and Human Rights 18(1): 115.

Robertson K et al., 2011. Rabies-related knowledge and practices among persons at risk of bat exposures in Thailand. PLoS Neglected Tropical Diseases 5(6): 1054.

Rodrigues RTFS et al., 2010. Biosensors as rapid diagnostic tests for tropical diseases. Critical Reviews in Clinical Laboratory Sciences 47(3): 139-169.

Schwarz NG et al., 2017. Microbiological laboratory diagnostics of neglected zoonotic diseases (NZDs). Acta Tropica 165: 40-65.

Shultz JM et al., 2016. The role of fear-related behaviors in the 2013–2016 West Africa Ebola virus disease outbreak. Current Psychiatry Reports 18: 1-14.

Souvenir R et al., 2007. An iterative method for selecting degenerate multiplex PCR primers. PCR Primer Design 2007: 245-267.

Sridhar S et al., 2015. A systematic approach to novel virus discovery in emerging infectious disease outbreaks. The Journal of Molecular Diagnostics 17(3): 230-241.

Stephanie K et al., 2001. Interactions between the rust fungus Puccinia punctiformis and ectophagous and endophagous insects on creeping thistle. Journal of Applied Ecology 38(3): 548-556.

Suwannarong K and Schuler S, 2016. Bat consumption in Thailand. Infection Ecology and Epidemiology 6: 29941.

Wolfe ND et al., 2007. Origins of major human infectious diseases. Nature 447: 279-283.

Woolhouse M and Gaunt E, 2007. Ecological origins of novel human pathogens. Critical Reviews in Microbiology 33(4): 231-242.

Woolhouse ME and Gowtage-Sequeria S, 2005. Host range and emerging and reemerging pathogens. Emerging Infectious Diseases 11(12): 1842.

World Health Organization, 1978. Ebola haemorrhagic fever in Zaire, 1976. Bull. World Health Organization 56: 271–293.

World Health Organization, 2016. International Health Regulations 2005. Geneva: World Health Organization.3rd Ed. Annual Reviews Animal Bioscience 6: 121-139.

Xu B et al., 2011. Metagenomic analysis of fever, thrombocytopenia and leukopenia syndrome (FTLS) in Henan Province, China: discovery of a new bunyavirus. PLoS Pathogens 7(11): 1002369.

Xu GJ et al., 2015. Comprehensive serological profiling of human populations using a synthetic human virome. Science 348: 0698.

Yu XJ et al., 2011. Fever with thrombocytopenia associated with a novel bunyavirus in China. New England Journal of Medicine 364(16): 1523-1532.

Zumla A et al., 2014. Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections—needs, advances, and future prospects. The Lancet Infectious Diseases 14(11): 1123-1135.

27

Sustainable Goals for Achieving Disease Control in Livestock and Animal Industry

AUTHORS DETAIL

Muhammad Asad[1]*, Saima Qadeer[1], Asma Ashraf[1], Sana Ullah[1], Ammara Riaz[2], Kashif Ali[1] and Sana Kausar[3]

[1]Department of Zoology, Division of Science & Technology, University of Education, Lahore Pakistan.
[2]Department of Life Sciences, Khwaja Fareed University of Engineering & Information Technology, Rahim Yar Khan.
[3]Department of Zoology, Government College University Faisalabad.
*Corresponding author: muhammad.asad@ue.edu.pk

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INTRODUCTION

Animals are our vital source of economy and contributes to the stability of our ecosystem. They integrate our economy by providing us milk, meat and other derivatives (Delucchi et al. 2022). Animals are also direct source of earning for our local farmers (Lam et al. 2019). Out of all economically benefitted animal's livestock sector is major contributor. Sustainability of humans depends upon the sustainability of these animals (Singh 2021). The need of the hour is to control the diseases of animals that may badly affect our economy (Compston et al. 2022). Globally near about 1 billion people take advantage from the livestock including Pakistan. This key driver contributes 11.7% to the total GDP of Pakistan and nearly 60% of total agriculture sector (Hussain et al. 2022).

The disease control and prevention need statistics on the morbidity and mortality of animals. In developed countries the disease surveillance system is also well developed and can be viewed as "early warning system". In developing countries such as Pakistan the surveillance system is not developed and unable to give desire information for better management of animal diseases (Akhtar and White 2003). Our health care system can't be improved overnight. Pakistan needs a long-term strategic plan with highly experienced team along with financial support (Hamid et al. 2014) The structure of reporting is also not well managed due to underreporting of positive cases by the healthcare workers. In Pakistan we need passive surveillance system instead of active surveillance system and moves towards active surveillance by offering better job paybacks and salaries to epidemiologists to attain the best out of the already prevailing tools (WHO 2006).

The diseases control mainly involves three different methods (i) Preventions (ii) Medications and (iii) Vaccines. The surveillance data helps the epidemiologists to understand the eruption of new pathogens, disease pattern and eradication of diseases. Many research centers in Pakistan focus on diagnostic services and etiology of diseases. There is need to improve the running animal healthcare system and equip it with latest tools and techniques and also needs to start the awareness campaigns among farmers to aware them about different animal diseases, their control, preventions and treatments (Birner et al. 2021) Fig. 1 illustrate different control measures to be used in the management of animal diseases.

Prevention of Environmental Contaminants

Environmental contamination plays an important role in spread of diseases in animals and poses health risk. Now a day's pollution is major contributor of health abnormalities in animals and other life forms (Chowdhary et al. 2020). Pollution is a naturally occurring process as many gases and crude oil keep leaking out from below the Earth surface and add up in the environment, thereby increasing the level of contamination. Many hazardous gases and toxic substances are present in the volcanic outputs, a natural phenomenon that occurs without any anthropogenic stimulus (Kumari et al. 2019). However, during the past few hundred years, both the concentration and variety of contaminants have skyrocketed due to the anthropogenic activities which intensified industrialization and burning of fuels in the recent times (Hong et al. 1996). This has led to an increase in the heavy metals and other pollutants in the environment, making it unhealthy for the living beings (Waldron and Edling 1977; Patra and Swarup 2000).

Agriculture sector is one of the major motives behind the recent surge in the levels of contaminants in the environment. Many pesticides such as Dichlorodiphenyltrichloroethane (DDT) are utilized to boost up the agricultural production (Rhind 2005). At the same time, the pesticides have been reported to cause diseases such as Parkinson's disease. Phthalates such as Diethylhexyl phthalate (DEHP), Dibutyl phthalate (DBP) and Monobutyl phthalate (MBP) are used as softening agents in the manufacturing of polyvinyl chloride plastics. Their exposure is associated with different cardiovascular, liver and urological abnormalities (Singh and Li 2011).

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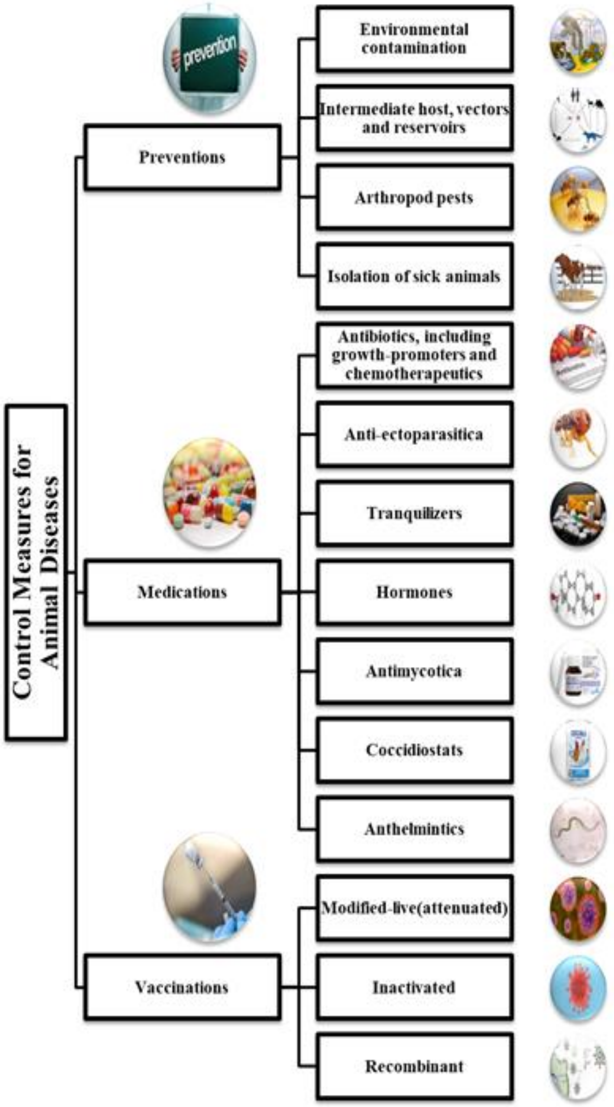
Control Measures for Animal Diseases
prevention
Preventions
Environmental contamination
Intermediate host, vectors and reservoirs
Arthropod pests
Isolation of sick animals
Medications
Antibiotics, including growth-promoters and chemotherapeutics
Anti-ectoparasitica
Tranquilizers
Hormones
Antimycotica
Coccidiostats
Anthelmintics
Vaccinations
Modified-live(attenuated)
Inactivated
Recombinant

Fig. 1: Different control measures for animal diseases

Given below are some of the recommendations to curtail the level of the pollution:

1- Grow trees because hazardous chemicals settle down on the leaves which filter them out through their stomata, thereby improving the air quality.

2- Pesticides and all sorts of agricultural chemicals should not be used in areas that are in close vicinity of animal farms. The runoff of these chemicals gets mixed with the drinking water and contaminates the grazing areas of the fauna.

3- Animals should not be allowed to graze in areas where sludge and other chemical wastes from treatment plants are deposited.

4- Animal farms should not be made near fertilizer, ceramic, cement, copper and other such factories.

5- Vehicles should be maintained to prevent oil leaks as it is also toxic to farm animals.

Prevention from Intermediate Host, Vectors and Reservoirs

Diseases transferred by vectors and intermediate hosts are a subject of great concern. The climate change has further made the life easier for these vectors (Medlock and Leach 2015). The impacts of these infections vary between animals. Some are more susceptible while others show immunity. Many of these infections are zoonotic in nature (Hansford et al. 2017). Taking the precautionary measures and preventing the spread of the infection in fauna is the most effective method for the containment and management of the disease (Wobeser 2002). Given below the practices that needs to be adopted in order to contain the infections in animals:

1- Effective and timely detection followed by quick response mechanism is the key to prevent the spread of infection in animals.

2- The newly purchased animals should be screened and scrutinized before introduction into the farm.

3- Proper hygienic conditions should be ensured with respect to food and water.

4- Intermediate hosts should be properly taken care of through suitable control method.

5- Reduce the intermediate and reservoir hosts by farm management practices.

6- Initiate and maintain vaccination program for control of vector population.

Control of Arthropod Pests

Mosquitos, ticks, deer flies, aphids and some of the spiders are among the arthropods that infect the animals. Infections transmitted through these arthropods can negatively affect the economic production of the livestock (Steelman 1976: Espinosa et al. 2020) These infections seriously disturb the health and fitness of the animals, thereby leading to decrease in production and increase in mortality (Steelman 1976; Quadros et al. 2020).

Effective management and containment practice are those that protect environment, human and animal life at the same cost (Kogan 1998). It involves careful monitoring and control strategies to mitigate the growth of pest species of arthropods, with the least economic costs possible. The control strategies can be chemical, biological or a combination of both. At the same time, integrated pest management programs can also help to mitigate the pest population and minimize their growth (Brenner et al. 2003).

Following measures should need to be taken to prevent the arthropods pest to maintain the animal health.

1- Manure, stagnant water garbage and other places that can act as the breeding places of insects should be removed or cleaned periodically.

2- Cracks and crevices that act as the egg deposit site should be removed.

3- Regular sprays should be done to prevent the growth of infection causing insects such as mosquitos and flies.
4- The areas inside and around the vicinity of animal farms should be properly cleaned and kept dry as moisture promotes the growth of these insects.

Isolation of Sick Animals

Timely isolation of sick animals can prevent the spread of the disease and other animals from getting infected (Li et al. 2020). The animals which are reported to be infected or suspected to be infected should be segregated from the rest. The infected animals should be quarantined in isolation rooms which in turn should be located far away from the healthy livestock (McKenna et al. 2006).

Medication

Antibiotics

Antibiotics are antimicrobial agents that help to improve growth rate in poultry and livestock by inhibiting and destroying bacterial and fungal growth. They actively fight against animal disease, improve food conversion efficacy of animal and weight gain ultimately leading towards more productive and healthier animal growth (Dibner and Richards 2005). Now days, broad spectrum antibiotics are commonly in practice for farm animals to reduce illness because of limitations in identifying target pathogen for a specific antibiotic agent (Callaways et al. 2003). Multiple antibiotics have been administered for therapeutic purpose in agricultural farming as an alternative control strategy for livestock diseases including enteric diseases, mastitis, and respiratory tract disorders (Radostits et al. 2007). These antibiotics are also widely used in poultry against chronic respiratory disorders, fowl cholera, necrotic enteritis, avian influenza, and gangrenous dermatitis (Harrison and Bratcher 2008).

Antibiotics as Growth Promoters

Growth promoters are the products that help an animal to grow faster form the same amount of food intake in a given period of time. Antibiotics as growth promoters in livestock have been used since 1950s, in Australia, several European countries and United States (Dibner and Richards 2005). Beta-lactame antibiotics particularly lincosamide and penicillins, as well as macrolides particularly tetracyclines and erythromycin are commonly being employed as growth promoters of Pigs in United States (Peter and John 2004). Similarly, number of antimicrobial agents including flavophospholipol, virginiamycin, arsenic compounds, quinoxalines, pleuromutilins and bacitracin are used in United States as growth promoters (Peter and John 2004). In Australia such growth promoters are in practice for agriculture animals (JETACAR 1999). Monensin, flavophospholipol and virginiamycin antibiotics are also used as growth promoters in cattle industry. These promoters play a major role to improve milk production and stimulate muscles growth in United States (Peter and John 2004). Antibiotics like monensin and lasalocid are considered as most effective and safe growth promoters due to their antibacterial ability against lactate producing species instead of producing any harm to lactate fermenters. Similar antibiotics are also in practice in Australian cattle farmers as growth promoters (JETACAR 1999; Dibner and Richards 2005). In United States, virginiamycin and flavophospholipol are employed as specific growth promoters in poultry industry for increased egg and meat production (Peter and John 2004) whereas flavophospholipol, virginiamycin and bacitracin and arsenic compound are also used in Australian poultry industry (JETACAR 1999). Similarly, major growth promoters in Europe poultry industry include virginiamycin, avoparcin, bacitracin and avilamycin. Recently, it was reported that addition of 10mg/kg avoparcin increased chicken meat growth rate by 2.37%, feed conversion efficacy by 2.96% and increase per kg live weight by 1.33%. Likewise, virginiamycin (17.6mg/kg) increased chicken meat growth rate by 3.48%, feed conversion efficacy by 3.19% and increase per kg liveweight by 1.48% respectively (Mehdi et al. 2011).

Parasiticides

Ectoparasites cause a serious loss to livestock production globally. Moreover, these ectoparasites also act as an agent of zoonotic diseases. These ectoparasiticides can be used directly to the animals or their introduction in the environment could be a suitable approach to control parasitic infestation or vector population to a level that reduce economic loss by improving health of livestock. Ectoparasiticides are classified based on their structure, nature and mode of action including pyrethroids, pyrethrins, carbamates, macrocyclic lactones (milbemycines and avermectins) formamidines, organophosphates, organochlorines and insect growth regulators. These ectoparasiticides act as neurotoxins, targeting nervous system of parasites and paralyze them. These are applied directly or indirectly in lager animals to reduce ectoparasites number and enhance growth rate (Taylor 2005).

Hormones

Currently hormones are widely used as a growth promoter in animal industry particularly for cattle industry in Canada, United States and Australia. These are being employed for increased feed efficiency and best gain (Qaid and Abdoun 2022). The hormones are administered to the animals in the form of capsules implanted behind the ears under the skin.

These capsules release a required dose of hormone after a regular interval of time and found to increase meat production during all stages of growth (Platter et al. 2003). Generally, the hormones that are used for food animals are classified as natural hormones; derived directly from animals or humans and synthetic hormones; chemically synthesized that has the ability to mimic the function of natural hormones (Cepeda and Fente 2012). Testosterone, estradiol, and progesterone are the natural hormones whereas TBA and zeranol are synthetic. The hormone MGA mimics the action of progesterone, TBA mimics the testosterone and zeranol has the ability to mimic the biological activity of estradiol (Passantino 2012). Estradiol promotes the growth of the farm animals by increasing appetite ultimately improving the feed conversion efficacy. Similar effects have been reported previously that testosterone alone or in combinations with other hormones enhanced the feed conversion efficiency and body weight gain (Kefi 2014).

Coccidiostats

Coccidiosis is protozoan parasitic disease caused by various species of *Eimeria* in poultry and livestock and results into massive economic loss due to increased mortality rate and high veterinary cost among the infected animals (Chartier and Paraud 2012). Coccidiostats are chemical agents that are used globally for the treatment of coccidiosis in animal farming especially for reared species of sheep and cattle (Chartier and Paraud 2012; Clarke et al. 2014). Coccidiostats are classified as naturally occurring polyether ionophores including salinomycin, narasin, maduramicin, monensin and lasalocid as well as synthetic coccidiostats including diclazuril, halofuginone, nicarbazin and robenidine (Dubreil-Chéneau et al. 2009).

Anthelmintics

Helminthes cause the serious infection of gastrointestinal tract in animals and prove to be a serious limitation for livestock production worldwide (Githiori et al. 2004). Gastrointestinal nematodes, liver flukes and lungworms parasitize cattle and cause serious diseases. Ultimately these pathogens effects productivity in livestock. These are production limiting diseases and all classes of grazing ruminants are affected. The impacts of these diseases are very severe and leads to subclinical infections resulting in loss of fertility, less milk yield and reduced growth (Morgan et al. 2013). Similarly, lungworms cause acute infection with high mortality rate and rapid decrease in milk production (Holzhauer et al. 2011). Anthelmintics are the chemical agents that reduce the parasite number by inhibiting their growth, paralyzing them or by killing them. Good anthelmintics have broad range of activity against all stage of parasite and easy to apply on larger animals, have high safety range and have no undesirable side effects (Enejoh and Suleiman 2017). Doramectin, abamectin, eprinomectin and ivermectin are commonly used for the treatment of infection caused by helminths in livestock whereas moxidectin is particularly used against helminthic infection in cattle (Moreno and Lanusse 2017).

Tranquilizers

Tranquilizers are medicines that are used to reduce anxiety among the animals by controlling aggressive behavior. They do not provide any pain relief. Animals that are treated with tranquilizers behave calmer and more relaxed instead of being aware of their surroundings (Yeh et al. 2022) Tranquilizers that are administered to the livestock are mainly grouped into two categories. Minor tranquilizers helps to fight against anxiety e.g. diazepam whereas major tranquilizers are administered to increase relaxation e.g. acepromazine (Papich 2020). Commonly used tranquilizers include detomidine, acepromazine, xylazine, butorphanol and romifidine. These are administered to animals intravenously but can also be injected intramuscularly. These cause tranquilization within minutes and behave as fast acting tranquilizers (Leonardi et al. 2020).

Antimycotics

Mycotic infections are caused by fungi in animals. Number of fungi attack animal body surfaces and cause infection. Antimycotics are the agents that are applied superficially on mucus membranes, skin, in eyes or ears to control fungal infections (Ivanov et al. 2022) Commonly used antimycotics include sulfur preparations (benzoyl disulfide, monosulfiram), iodine preparations (iodohors, tincture of iodine and potassium iodide), phenols (thymol, phenol) copper preparations (cuprimyxin, copper sulfate and copper naphthenate), organic acids (salicyclic acids, benzoic acid), fatty acid and salts (undecylenates, propionates) (Rochette et al. 2003).

Vaccination

Vaccination is one of the most operative ways to diminish the burden of diseases in farm animals, pets, and wild animals (Volz et al. 2015; Haagmans et al. 2016). It is one of the key tools to maintain animal welfare and ensuring their health (Carpenter et al. 2022). Therefore, the use of vaccines is continuously increasing in animal disease control and prevention programs. However, it is demanded to develop safe and effective vaccines through innovative research that are effective as a vital medicine and capable of preventing, mitigating, recuperating, or alleviating the clinical symptoms of animal diseases, and keeping in view the risk posed to humans as well (Negrón et al. 2019). Such vaccines are particularly important for complex diseases with limited or no treatment options and are often prioritized for preventing and minimizing the disease clinical signs. Furthermore, these vaccines should be cost-effective and capable of saving human lives, improving food quality by improving animal health, and uplifting the economy (Monath 2013).

Keeping in view the emerging and re-emerging diseases of animals (such as MERS-CoV and influenza group), several effective vaccines have been designed and widely manufactured (Singh et al. 2018; Adney et al. 2019). These vaccines are employed for certain endemic and exotic diseases as these still pose a risk of entering any territory, affecting animals there and humans as well (Monath 2013; Dominguez et al. 2016). Therefore, animal medicine sectors have generously invested in research for developing veterinary vaccines to cope with different endemic and exotic animal diseases (History of Vaccine 2022). It is due to their efforts that diseases like rinderpest (which devastated livestock in the past around the globe) have been eradicated completely in 2011 (OIE 2011). Although vaccine development has led to successful control of many diseases, however, it is very difficult to develop effective vaccines on account of the complex nature of both the inherent nature of the pathogens and vaccine development (Singh et al. 2018; Head et al. 2019; Carpenter et al. 2022). Yet, a plethora of research is being conducted to develop vaccines that can tackle veterinary pathogens and help in maintaining animal health (Francis 2022). The developed vaccines are updated from time to time to protect the animals against new strains of pathogens (Corbett et al. 2020).

Vaccines are used in animal husbandry to stimulate the immune response in animals without affecting them (Roth 2011). These vaccinated healthy animals respond to vaccines and remember the pathogen for which they were vaccinated (McAloose et al. 2020). Therefore, vaccinated animals are expected to be protected from certain diseases upon exposure (Paul-Pierre 2012).

Vaccines are available in a variety and hence they are categorized as inactivated (killed; Type I Vaccine Technologies), modified-live (attenuated; Type II Vaccine Technologies), subunit (Type III Vaccine Technologies), recombinant (Type IV Vaccine Technologies) and toxoid vaccines. Modified-live vaccines contain a weakened but intact pathogen that can enhance or elicit an immune response; however, they do not lead to any clinical disease (Wallace et al. 2020). Inactivated vaccines contain pathogens, which are completely inactivated and are not infectious anymore. This type of vaccine is added with an adjuvant to improve the protective responses of the immune system (Keshtkar-Jahromi et al. 2020). Recombinant vaccines are produced via genetic engineering technology. This type of vaccine is prepared by extracting certain genetic material from the pathogens that produce certain proteins, eliciting immune responses in the animals after they are vaccinated (European Medicines Agency 2016). Toxoid vaccines are prepared from inactivated toxins isolated from the pathogen for stimulating immune responses and protecting the animals against the same toxins (Rabadi and Brady 2022). In the modern era of cutting-edge research and innovation, different novel and sophisticated vaccines are developed including marker vaccines. An example is the marker vaccine for a highly contagious disease of cattle, Infectious Bovine Rhinotracheitis (IBR). Apart from this, dietary vaccines have been developed in the past decade. Nano-carriers based vaccines gained substantial attention, for example, synthetic materials such as polyethylene glycol and poly-L-lactic acid, and natural materials such as cellulose derivatives, chitosan, and alginate are used (Patra et al. 2018; Pumchan et al. 2022).

Regardless of the vaccine or vaccine type, certain points should be kept in mind while vaccinating animals. These points include; (1) the animal should be in good health to ensure the proper functioning of the immune system of the animals; (2) booster vaccination should be employed at regular intervals to boost and maintain the immunity as per the veterinary advice; (3) vaccination protocol and vaccines should be adopted concerning the animal or animal's group such as their age, movement, lifestyle, travel, prevailing disease, etc.; (4) herd immunity by vaccinating a high proportion of the population; (5) prioritizing zoonotic diseases; (6) viral diseases are often followed by bacterial diseases therefore along with antibiotic for the bacterial disease employing vaccines is highly recommended as vaccination for both viral and bacterial diseases preserve the effectiveness of the antibiotics (Ferguson et al. 2016; NOAH 2017; Joseph et al. 2017; Singh et al. 2018; CDC 2021; Alharbi et al. 2022; Carpenter et al. 2022).

In feline vaccination, many important diseases in cats are alleviated, prevented, and controlled via vaccination such as feline panleukopenia or parvovirus, feline calicivirus, feline herpesvirus, feline rabies, feline leukaemia virus, etc. (NOAH 2017). In canine vaccination, different vaccines are developed for important diseases of dogs such as canine distemper virus, canine parainfluenza virus, canine leptospira, canine adenovirus, canine parvovirus, rabies, etc. (VMD 2018; Wallace et al. 2017; Wallace et al. 2020). Vaccines against rabbit haemorrhagic diseases, myxomatosis and HIV are developed for rabbits' vaccination (Pollara et al. 2019). Several vaccines are being used for farm animals as well such as bovine viral diarrhea in cattle, and vaccines against Bacterium salmonicida, Streptococcosis disease, *E. coli*, *Bacillus subtilis*, *Lactococcus lactis*, etc. (Heath et al. 2012; Munang'andu et al. 2016; Yao et al. 2019; Cai et al. 2020; Zhang 2021; Pumchan et al. 2022). Equine vaccines are also widely adopted such as vaccines for equine herpes virus 1, equine herpes virus 4, tetanus, and equine influenza virus (Singh et al. 2018; Oladunni et al. 2021; BEVA 2023). Responsible use of medicines in agriculture alliance (RUMA) issues species-specific guidelines from time to time (RUMA 2023).

Conclusion

The global food scarcity and rising inflation are major concerns, and the livestock sector in Pakistan, which accounts for a significant portion of the country's GDP, is facing threats from various animal diseases. A well-integrated approach is needed to address these issues, including public awareness and vaccination strategies, to prevent economic outbreaks and ensure safe and secure livestock production in the future.

REFERENCES

Adney DR et al., 2019. Efficacy of an Adjuvanted Middle East Respiratory Syndrome Coronavirus Spike Protein Vaccine in Dromedary Camels and Alpacas. Viruses 11: 212.

Akhtar S and White F, 2003. Animal disease surveillance: prospects for development in Pakistan. Revue Scientifique et Technique-Office International Des Épizooties 22(3): 977-988.

Alharbi NK et al., 2022. Immunogenicity of High-Dose MVA-Based MERS Vaccine Candidate in Mice and Camels. Vaccines 10: 1330.

BEVA, 2023. Maintaining a healthy horse. British Equine Veterinary Association (Guidelines). Available at https://www.beva.org.uk/Resources-For-Owners/Guidance/Maintaining-A-Healthy-Horse . Accessed on Jan 15th, 2023.

Birner et al., 2021. Who drives the digital revolution in agriculture? A review of supply-side trends, players and challenges. Applied Economic Perspectives and Policy 43(4): 1260-1285.

Brenner BL et al., 2003. Integrated pest management in an urban community: a successful partnership for prevention. Environmental Health Perspectives 111: 1649-1653.

Cai YZ et al., 2020. Oral immunization with surface immunogenic protein from Streptococcus agalactiae expressed in Lactococcus lactis induces protective immune responses of tilapia *Oreochromis niloticus*. Aquaculture 18: 100538.

Callaways TR et al., 2003. Forage feeding to reduce preharvest Escherichia coli populations in cattle, a review. Journal of Dairy Science 86(3): 852-860.

Carpenter A et al., 2022. Vaccine Preventable Zoonotic Diseases: Challenges and Opportunities for Public Health Progress. Vaccines 10: 993.

CDC (Centers for Disease Control and Prevention), 2021. Centers for Disease Control and Prevention Strategic Framework for Global Immunization, 2021–2030; Centers for Disease Control and Prevention: Atlanta, GA, USA.

Cepeda A and Fente CA, 2012. Natural hormones in food-producing animals: legal measurements and analytical implications. In: Regal P, Cepeda A, Fente CA, editors. Food production-approaches, challenges and tasks. Fente University of Santiago de Compostela (Spain): In Tech; pp: 203-205.

Chartier C and Paraud C, 2012. Coccidiosis due to Eimeria in sheep and goats, a review. Small Ruminant Research 103(1): 84-92.

Chowdhary P et al., 2020. Role of industries in water scarcity and its adverse effects on environment and human health. Environmental Concerns and Sustainable Development 2020: 235-256

Clarke L et al., 2014. A review of coccidiostats and the analysis of their residues in meat and other food. Meat Science 97(3): 358-374.

Compston P et al., 2022. A systematic review of the methods used to analyse the economic impact of endemic foot-and-mouth disease. Transboundary and Emerging Diseases.

Corbett KS et al., 2020. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature 586: 567–571.

Delucchi AS et al., 2022. Becoming a ‘good producer’in the agri-environmental project economy. Journal of Rural Studies 96: 207-216.

Dibner JJ and Richards JD, 2005. Antibiotic growth promoters in agriculture: history and mode of action. Poultry Science 84(4): 634-643.

Dominguez M et al., 2016. Equine disease events resulting from international horse movements: Systematic review and lessons learned. Equine Veterinary Journal 48: 641–653.

Dubreil-Chéneau E et al., 2009. Validation of a multi-residue liquid chromatography–tandem mass spectrometry confirmatory method for 10 anticoccidials in eggs according to Commission Decision 2002/657/EC. Journal of Chromatography A 1216(46): 8149-8157.

Enejoh OS and Suleiman MM, 2017. Anthelmintics and their application in veterinary medicine. Research in Medical & Engineering Sciences 2(3).

Espinosa R et al., 2020. Infectious diseases and meat production. Environmental and Resource Economics 76(4): 1019-1044.

European Medicines Agency, 2016. Letifend Canine Leishmaniasis Vaccine (Recombinant Protein). Available online: https://www.ema.europa.eu/en/documents/overview/letifend-epar-summary-public_en.pdf . Accessed on Jan 15th, 2023.

Ferguson L et al., 2016. Pathogenesis of influenza D virus in cattle. Journal of Virology 90: 5636–5642.

Francis MJ, 2022. Considerations for rapid development and licensing of conventional and platform technology veterinary vaccines. Avian Pathology 51: 107–122.

Githiori JB et al., 2004. Evaluation of anthelmintic properties of some plants used as livestock dewormers against Haemonchus contortus infections in sheep. Parasitology 129(2): 245-253.

Haagmans BL et al., 2016. An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels. Science 351: 77–81.

Hamid S et al., 2014. Job satisfaction among nurses working in the private and public sectors: a qualitative study in tertiary care hospitals in Pakistan. Journal of Multidisciplinary Healthcare 7: 25.

Hansford KM et al., 2017. Rhipicephalus sanguineus importation into the UK: surveillance, risk, public health awareness and One Health response. Veterinary Record 180: 119.

Harrison CJ and Bratcher D, 2008. Cephalosporins: a review. Pediatrics in Review 29(8): 264-273.

Head JR et al., 2019. Wallace, R. Environmental distribution of certain modified live-virus vaccines with a high safety profile presents a low-risk, high-reward to control zoonotic diseases. Scientific Reports 9: 6783.

Heath DD et al., 2012. Maternal antibody parameters of cattle and calves receiving EG95 vaccine to protect against Echinococcus granulosus. Vaccine 30: 7321-7326.

History of Vaccine, 2022. Vaccine Development, Testing, and Regulation. Available online: https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation. Accessed on January 15th, 2023.

Holzhauer M et al., 2011. Lungworm outbreaks in adult dairy cows: estimating economic losses and lessons to be learned. Veterinary Record 169(19): 494.

Hong S et al., 1996. History of ancient copper smelting pollution during Roman and medieval times recorded in Greenland ice. Science 272: 246-249.

Hussain S et al., 2022. Spatio-temporal distribution of identified tick species from small and large ruminants of Pakistan. Biologia 77(6): 1563-1573.

Ivanov M et al., 2022. Emerging Antifungal Targets and Strategies. International Journal of Molecular Sciences 23(5): 2756.

Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) Report, 1999. The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans. Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), October 1999. Canberra, ACT: Department of Health.

Joseph U et al., 2017. The ecology and adaptive evolution of influenza A interspecies transmission. Influenza and Other Respiratory Viruses 11: 74–84.

Kefi AS, 2014. Influence of dietary soya beans (glycine max(l.) merr.) protein and lipid combination, and androgen (17 α–methyl testosterone) levels on the growth and reproduction of Oreochromis andersonii (Castelnau, 1861). PhD Dissertation, Bunda College of Agriculture, University of Malawi.

Keshtkar-Jahromi M et al., 2020. The Western Equine Encephalitis Lyophilized, Inactivated Vaccine: An Update on Safety and Immunogenicity. Frontiers in Immunology 11: 2676.

Kogan M, 1998, Integrated pest management: historical perspectives and contemporary developments. Annual Review of Entomology 43: 243–270.

Kumari WG et al., 2019. Sustainable development of enhanced geothermal systems based on geotechnical research–A review. Earth-Science Reviews 199: 102955.

Lam Y et al., 2019. Applying an environmental public health lens to the industrialization of food animal production in ten low- and middle-income countries. Globalization and Health 15(1): 1-20.

Leonardi F et al., 2020. Effects of intravenous romifidine, detomidine, detomidine combined with butorphanol, and xylazine on tear production in horses. Equine Veterinary Education 32: 53-57.

Li Y et al., 2020. African swine fever in a commercial pig farm: Outbreak investigation and an approach for identifying the source of infection. Transboundary and Emerging Diseases 67(6): 2564-2578.

McAloose D et al., 2020. From People to Panthera: Natural SARS-CoV-2 Infection in Tigers and Lions at the Bronx Zoo. mBio 11: e02220.

McKenna SLB et al., 2006. Johne's disease in Canada part II: disease impacts, risk factors, and control programs for dairy producers. Canadian Veterinary Journal 47: 1089-1099

Medlock JM and Leach SA, 2015. Effect of climate change on vector-borne disease risk in the UK. The Lancet Infectious Diseases 15: 721–730.

Mehdi et al., 2018. Use of antibiotics in broiler production: Global impacts and alternatives. Animal Nutrition 4(2): 170-178.

Monath TP, 2013. Vaccines against diseases transmitted from animals to humans: A one health paradigm. Vaccine 31: 5321–5338.

Moreno L and Lanusse C, 2017. Specific veterinary drug residues of concern in meat production. In: Purslow P, editor. New aspects of meat quality: Woodhead Publishing; pp: 605-627.

Morgan ER et al., 2013. Global Change and Helminth Infections in Grazing Ruminants: Impacts, Trends and Sustainable Solutions. Agriculture 3: 484–502.

Munang'andu HM et al., 2016. An overview of vaccination strategies and antigen delivery systems for Streptococcus agalactiae vaccines in Nile tilapia (Oreochromis niloticus). Vaccines 4: 48.

Negrón ME et al., 2019. Notes from the Field: Human Brucella abortus RB51 Infections Caused by Consumption of Unpasteurized Domestic Dairy Products United States, 2017–2019. Morbidity and Mortality Weekly Report 68: 185.

NOAH, 2017. Vaccination for animal health: an overview. National Office of Animal Health Ltd. Available at https://www.noah.co.uk/topics/farm-animals/vaccination-for-animal-health/. Accessed on Jan 15th, 2023.

OIE, 2011. The Odyssey of rinderpest eradication. World Organisation for Animal Health. Available at https://www.woah.org/en/the-odyssey-of-rinderpest-eradication/. Accessed on Jan 15th, 2023.

Oladunni FS et al., 1657. Equine Influenza Virus and Vaccines. Viruses 13: 1657.

Papich MG, 2020. Papich Handbook of Veterinary Drugs-E-Book. Elsevier Health Sciences.

Passantino A, 2012. Steroid hormones in food producing animals: Regulatory situation in Europe. A bird's-eye view of veterinary medicine. 22: 33-50.

Patra JK et al., 2018. Nano based drug delivery systems: Recent developments and future prospects. Journal of Nanobiotechnology 16: 71.

Patra RC and Swarup D, 2000. Effect of lead on erthrocytic antioxidant defense, lipid peroxide level and thiol group in calves. Research in Veterinary Science 68: 71-74.

Paul-Pierre P, 2012. Role of Vaccination in Animal Health. Bulletin de l'Académie Nationale de Médecine 196: 589–620.

Peter H and John H, 2004. Food and Agriculture Organization; USA: Antibiotic Growth-Promoters in Food Animals.

Platter W et al., 2003. Effects of repetitive use of hormonal implants on beef carcass quality, tenderness, and consumer ratings of beef palatability. Journal of Animal Science 81: 984–996.

Pollara J et al., 2019. Bridging vaccineinduced HIV-1 neutralizing and effector antibody responses in rabbit and rhesus macaque animal models. Journal of Virology 93: e02119-18.

Pumchan A et al., 2022. A Novel Efficient Piscine Oral Nano-Vaccine Delivery System: Modified Halloysite Nanotubes (HNTs) Preventing Streptococcosis Disease in Tilapia (Oreochromis sp.). Vaccines 10: 1180.

Qaid MM and Abdoun KA, 2022. Safety and concerns of hormonal application in farm animal production: a review. Journal of Applied Animal Research 50(1): 426-439.

Rabadi, T and Brady MF, 2022. Tetanus Toxoid. Available at https://www.ncbi.nlm.nih.gov/books/NBK557415/. Accessed on Jan 15th, 2023.

Radostits OM et al., 2007. A textbook of the diseases of cattle, horses, sheep, pigs and goats. Veterinary Medicine 10: 2045-2050.

Rhind SM, 2005. Are endocrine disrupting compounds a threat to farm animal health, welfare and productivity? Reproduction in Domestic Animals 40: 282-290.

Rochette F et al., 2003. Antifungal agents of use in animal health–practical applications. Journal of Veterinary Pharmacology and Therapeutics 26(1): 31-53.

Roth JA, 2011. Veterinary Vaccines and Their Importance to Animal Health and Public Health. Procedia in Vaccinology 5: 127-136.

RUMA, 2023. Responsible use of medicine in agriculture alliance. Available at https://www.ruma.org.uk/vaccines/. Accessed on Jan 15th, 2023.

Singh M, 2021. Organic farming for sustainable agriculture. Indian Journal of Organic Farming 1(1): 1-8.

Singh RK et al., 2018. A Comprehensive Review on Equine Influenza Virus: Etiology, Epidemiology, Pathobiology, Advances in Developing Diagnostics, Vaccines, and Control Strategies. Frontiers in Microbiology 9: 1941.

Singh S and Li SSL, 2011. Phthalates: toxicogenomics and inferred human diseases. Genomics 97(3): 148-157.

Steelman CD, 1976. Effects of external and internal arthropod parasites on domestic livestock production. Annual Review of Entomology 21: 155–178.

Taylor MA, 2005. Ectoparasiticides used in large animals. In: Aiello SE, editor. The Merck Veterinary Manual: Merck and Co., Inc. Whitehouse Station, USA; pp: 2158-2165.

VMD, 2018. VMD position paper on authorized vaccination schedules for dogs. Veterinary Medicines Directorate, Government of UK

Volz A et al., 2015. Protective Efficacy of Recombinant Modified Vaccinia Virus Ankara Delivering Middle East Respiratory Syndrome Coronavirus Spike Glycoprotein. Journal of Virology 89: 8651-8656.

Waldron HA and Edling C, 1977. Occupational Health Practice, 4th Ed., Butterworth Heinemann, Oxford.

Wallace RM et al., 2017. Elimination of Dog-Mediated Human Rabies Deaths by 2030: Needs Assessment and Alternatives for Progress Based on Dog Vaccination. Frontiers in Veterinary Science 4: 9.

Wallace RM et al., 2020. Role of Oral Rabies Vaccines in the Elimination of Dog Mediated Human Rabies Deaths. Emerging Infectious Diseases 26: e201266.

Wobeser G, 2002. Disease management strategies for wildlife. Review of Science and Technology 21: 159-178.

World Health Organization, 2006. The world health report 2006: working together for health.

Yao YY et al., 2019. Oral vaccination of tilapia against Streptococcus agalactiae using Bacillus subtilis spores expressing Sip. Fish and Shellfish Immunology 86: 999-1008.

Yeh YM et al., 2022. Effects of Lactiplantibacillus plantarum PS128 on alleviating canine aggression and separation anxiety. Applied Animal Behaviour Science 247: 105569.

Zhang Z, 2021. Research advances on Tilapia streptococcosis. Pathogens 10: 558.

28

The Use of Viral Vectors in the Treatment of Diseases (Viral Vectors for Gene Therapy)

AUTHORS DETAIL

Azam Mokhtari[1] and Mohamad Javad Ataie[2]

[1]Department of Pathobiology, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord, Iran
[2]Department of Genetics, Faculty of Sciences, Shahrekord University, Shahrekord, Iran
*Corresponding author: a.mokhtari@alumni..ut.ac.ir

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INTRODUCTION

The idea of gene therapy began in the mid-20th century as a revolution in treatment with the commitment of treating any disease practically with a molecular basis. Today, gene therapy is a treatment method with the hope of curing many diseases that could not be treated with conventional methods. In gene therapy, a carrier is needed to deliver the gene therapy to the target cell. Viral vectors are considered to be the best vectors due to their high efficiency. After several decades of efforts, good outcomes have been obtained from the treatment of diseases such as cancer or infection by gene therapy with viral vectors (Escors and Breckpot 2010; Zhao et al. 2022).

Gene Therapy

Gene therapy is the modification of gene expression, the correction of defective genes and the treatment of monogenic diseases. Gene therapy, unlike old treatments, changes cells genetically. Another definition for gene therapy is to treat a disease or disorder by introducing remedial genes into the right cells. For prosperous gene therapy, the exogenous part of gene should enter the target cell correctly. The first clinical work of gene therapy in humans was performed in 1990 using a retrovirus vector for the treatment of severe combined immunodeficiency (SCID) disease (Escors and Breckpot 2010). After several cases of immune response and leukemia after gene delivery with a retroviral vector in 2000, the need to obtain safe viral vectors became apparent. After 2000, the world focused on better progress in gene therapy. These actions led to the first clinical approval of gene therapy products in 2003 for head and neck cancer in China. The European Medicines Agency and the United States of America unveiled their products in 2012 and 2017, respectively. The 2012 European Medicines Agency product was the first AAV- based gene delivery approved, and in 2017, FDA supported a lentiviral vector for the treatment of acute lymphoblastic leukemia. Recently, the therapeutic horizon of gene therapy has expanded rapidly and is now capable of treating a wider range of diseases. Today's gene therapies are divided into two categories: ex-vivo and in-vivo (Gowing et al. 2017; Zhao et al. 2022).

In-vivo gene therapy is introducing the genes into the bloodstream or the desired organs and ex-vivo gene therapy is the manipulation and genetic modification of the patient's cells outside the body to produce therapeutic factors and then transplant them to the target patient (Tomás et al. 2013).

The main reason for using viruses such as Ad, AAV, HSV, retrovirus, and lentivirus as a vector for gene transfer is their capability to infect cells and transfer the used genetic material to host cells (Zhao et al. 2022).

The Types of Common Viral Vectors

Lentivirus

Lentiviruses are a group of viruses with a lengthy incubation period of several months to several years. Lentiviruses are members of Retroviridae. Retroviruses are viruses with a genome consisting of two ss RNAs$^+$. These viruses are spherical in shape (Tomás et al. 2013).

In general, there are two types of retroviral vector systems:
1. Retroviral vectors derived from mouse leukemia virus
2. Lentiviral vectors derived from HIV-1

Today, unlike in the past, the use of the second method (LV) is more popular for several reasons such as; LVs can convert non-dividing cells into dividing cells due to their ability to translocate across the nuclear membrane, has a lower mutation rate than MLV, and can be produced at high concentration (Merten et al. 2016).

HIV-1 consists of three main genes, gag, pol, and env and several non-coding sequences. They also have the gag gene encodes structural proteins, pol encodes RNA dependent RNA-pol, and the env resposible for the syntesis of viral envelope proteins. The beginning of HIV-1's life is when the viral envelope (env) binds to a membrane receptor (CD4). Then, the virus releases into the cell. After the virus enters the cell, ssRNA is transcribed into dsDNA by the RT enzyme, which is called the provirus. Inside the nucleus, the provirus integrates with the cell genome. New mRNA transcripts enter the cytoplasm for translation from the nucleus, producing new immature virions that leave the cell by budding (Escors and Breckpot 2010; Tomás et al. 2013).

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Development of Lentivirus Vectors

In 1989, an HIV-1 provirus gene was constructed. Transduction of Jurkat cells with the modified provirus produced replicative infectious viruses very similar to wild-type HIV-1. A few months later, another study was designed that marked the beginning of the development of lentiviral vectors. This study demonstrated that a defective HIV-1 with its envelope removed could not cause infection. This development showed lentiviruses can be an option to deliver the desired genetic material to the cells (Zhao et al. 2022).

Currently, there are four generations of Lv vectors, which differ in the number of genetic structures, the number of wild-type genes, the types of heterologous elements, and vector immunity. The four mentioned generations are:

1. First generation: LVs have all structural proteins except env. The safety of this system is not high.
2. Second generation: to increase safety and reduce toxicity, all accessory genes that were not necessary for reproduction were removed in the laboratory.
3. Third generation: the tat gene was removed, and the rev gene was placed in a plasmid.
4. Fourth generation: RRE sequences were replaced with similar heterologous sequences, which increased the stability of transcripts.

Nowadays, gene therapy using lentiviral vectors is used in the treatment of several monogenetic diseases, including SCID-X1, ADA-SCID, ALD, WAS, X-CGD, MLD, beta-thalassemia and sickle cell disease (Abraham and Weiss 2004; Tomás et al. 2013; Merten et al. 2016).

Disadvantages and Advantages of Lentiviral Vectors

Its advantages include long-term activation of target cells and reduced mutagenicity, while its disadvantages include its limitation in carrying genetic cargo (Abraham and Weiss 2004; Tomás et al. 2013; Merten et al. 2016).

Adenovirus

Adenovirus is a type of DNA virus. This virus does not have an envelope and has a linear genome that have 57 serotypes and are classified in categories A-G. Differences in the capsid lead to different tropisms, and these different serotypes create a wide range of candidates for therapeutic vectors. Currently, among all the viral vectors, adenoviruses have the best gene transfer system, which are effective in a wide range of host sells. Adenovirus is the first DNA virus introduced into gene therapy. This virus is often used to transfer different genes into cells in clinical studies of oncolysis. It can also be used to develop anti-tumor immunity and produce vaccines against HIV and influenza (Lee et al. 2017; Yamamoto et al. 2017).

Adenoviruses enable effective gene transfer to a wide range of dividing and non-dividing cells, both in-vivo and in-vitro. Furthermore, the short expression time and current levels of combinatorial immunity against adenoviruses make it an excellent platform for vaccine development. The spread of adenoviruses in the community is one of their characteristics, which has led to almost universal immunity against them. The use of vectors derived from common adenovirus serotypes is prohibited by such immunity. Therefore, to create vectors, researchers have focused on uncommon serotypes such as 2 and 5. The advantage of adenovirus vectors over lentiviruses is the ability to deliver genes larger than 8kb, and their reluctance to integrate their genome into the host DNA. In episomal transfer, the host cell faces a lower risk of mutation, but because they do not integrate, they have transient expression. The genome of adenoviruses is linear, non-segmented, and surrounded by inverted ITR repeats at both ends. ITRs are independent of primase and play an important role in DNA replication. Another genetic element of adenoviruses is the packaging signal. These transcripts have a regulatory role and also play an important role in DNA replication (Lee et al. 2017; Yamamoto et al. 2017).

Fiber proteins that are present in adenoviruses play a role in binding. Hexon proteins make up most of the viral capsid. Spikes also associate with the capsid base protein and facilitate binding to host cell receptors. (Lee et al. 2017; Yamamoto et al. 2017).

Adenovirus vectors become more efficient over time. Today there are three generations of adenovirus vectors but to create more safety, modifications were made by removing the genes necessary for replication.

First generation: Using adenoviral vectors that do not have E1a and E1b regulatory genes. The absence of these genes led to the reduction of primary gene replication.

Second generation: In the second generation, other non-structural genes were removed. In this generation, the cytotoxicity was reduced, but it still caused immune responses in the body, leading to reduced efficacy.

Third generation: Includes high-capacity adenoviral vectors (HC-Adeno Vector) and helper-dependent Adeno Vectors (HD-Adeno Vector). In HC-AdV, all viral coding sequences are removed and cytotoxicity is minimized, thus enabling the long-term expression of therapeutic genes. This generation is the most promising adenovirus vector to date (Lee et al. 2017).

Recombinant Adenoviral Vector

The use of recombinant adenoviruses has made significant progress recently, creating an initial adenoviral vector, particularly one of the first generations, which is a difficult and time-consuming process. But recombination also has problems; such as the high length of the adenovirus genome, the shortage of unique and beneficial restriction sites and difficulties for vector construction. However, the direct ligation method significantly improved the conditions, but the ligation method is not usually used because its efficiency is down and the recombinant virus frequently needs to be purified from wild-type and transgenic viruses (St George 2003; Lee et al. 2017).

The newest method being done today is the AdEasy Adenoviral Vector System. This method includes cloning the favorable gene in a shuttle vector and transferring the gene to the adenovirus genome by an adenovirus packaging system (St George 2003; Lee et al. 2017).

Treatments Mediated by Adenovirus Vectors

Gene Therapy for Adenovirus-mediated Single-gene Diseases

The adenovirus vector was first used in-vivo in 1992 to treat the genetic liver disease alpha-1 antitrypsin A1TA deficiency. In this method, alpha-1 antitrypsin cDNA was successfully introduced into the livers of these patients. In parallel with this experiment, researchers were using A1TA to treat patients with fibrocystic lungs, but once it was identified that the CFTR gene causes this disease, researchers began studying the transfer of CFTR cDNA through adeno vectors. The researchers found that the response of the patients to this vector was unfavorable and caused immunogenic events. The death of the patient who was being treated raised concerns and researchers turned to less immunogenic vectors such as LV and AAV. But despite many problems, adenovirus vectors have regained attention in recent years (St George 2003; Lee et al. 2017). One of the important points is the use of strong immunogenic features of these vectors. These features are now used to target host immunity in vaccines.

Adenoviral Vectors as Anticancer Agents

There are three treatment groups for anticancer adenoviral vectors:

1. In the first group, adenoviruses that are defective in replication are used. Due to their immunogenic properties, these vectors are directly attracted to tumor cells to transduce immune-related genes and induce antitumor responses.
2. In this category, adenoviral vectors that are capable of replication are used. These vectors are used to multiply in cancer cells and induce oncolysis as a result of virus-induced cell lysis in cancer cells.
3. Another method involves directly inducing an intrinsic cytotoxic cascade, which results in apoptosis, by overexpressing cancer cells, tumor suppressor genes, or cytotoxic genes in cancer cells (St George 2003; Lee et al. 2017).

Adenoviral Vectors for Vaccine Development

Adenovirus vectors are involved in tuberculosis, Ebola, malaria, and influenza vaccine development. These vaccines stimulate cytotoxic T cells and humoral immunity. Preliminary findings indicated that the vaccine was well tolerated (St George 2003; Lee et al. 2017).

Advantages

1. It is the most effective tool for gene delivery in the body because most of the body's cells have the adenovirus receptor
2. Making a gutless adeno vector allows us to bypass the body's immunity
3. It is nearly clear how to use them safely (St George 2003; Lee et al. 2017)

Disadvantages

1. Due to the wide range of adeno receptors, it is difficult to deliver gene therapy with adeno vectors to the target cell
2. IV injection of adeno vectors leads to liver tropism
3. Their strong immunogen is the most problematic issue in the body (St George 2003; Lee et al. 2017)

Adeno-associated Virus (AAV)

Adeno-associated virus (AAV) belongs to the genus Dependoparvovirus of the Parvoviridae family. Its life cycle depends on a helper virus such as Adenovirus. AAV has ssDNA genome contains the genes Rep (Replication), Cap (Capsid), and Aap (Assembly). It also contains inverted terminal repeats (ITR) that help DNA replication and packaging. Sequences that are placed between ITRs include a mammalian promoter for the desired gene and a terminator. The capsid of this virus contains three types of subunits, VP1, VP2, and VP3 (Wang et al. 2019; Li and Samulski 2020).

Nowadays, AAV vectors have performed well in clinical trials for in-vivo gene therapy. The AAV vector has unique features, including high tropism, low immunostimulation, ease of production, non-pathogenic, most often does not integrate into the host chromosome. Because rAAV lacks the Rep gene, rAAV genome integration is greatly reduced. Therefore, it is ideal for specific gene therapy (Wang et al. 2019; Li and Samulski 2020).

An important point in rAAV design is the size of the expression cassette. According to the cassette results, less than 5 Kb is enough. rAAV vectors greater than 5 kb led to a large reduction in transgenic recombination efficiency (Wang et al. 2019; Li and Samulski 2020).

Studies showed that the immune response of the host body to AAV vectors can include both cellular and innate immunity. The level of CTL response of target cells depends on the level of specific capsid antigens presented on their cells and AAV dsRNA may excites the innate immune response (Wang et al. 2019; Li and Samulski 2020).

AAVs do not stimulate the immune system very much. The reason for this is not fully understood, but AAV does not contain any viral genes, so it has no active viral genes to enhance the host's immune response. However, these AAV vectors have little immunogenicity, while capsid proteins and nucleic acid sequences can stimulate the host's immune system. But interesting results in clinical trials have shown that people who have been previously exposed to AAV can mount an immune response to the introduced vector, and this has become a major challenge in how to deliver safe rAAV (Wang et al. 2019; Li and Samulski 2020).

Gene Therapy Drugs with AAV

Ophthalmic diseases, Hemophilia, neurological diseases such as Parkinson's disease, including AADC deficiency, has been treated with AAV vectors. Several other diseases, such as heart disease and muscular diseases are also being researched in clinical trials (Wang et al. 2019; Li and Samulski 2020).

Baculovirus

The Baculoviruses belonging to the family Baculoviridae, are a group of DNA viruses that are pathogenic to insects. These viruses have small, rod-shaped structures. The word “baculovirus” is derived from the Latin word “baculum,” meaning “staff,” which indicates the shape of this virus. Baculoviruses are safe and non-toxic vectors with high replication capacities. The advantages of these viruses include infecting stationary and proliferating cells and being very compatible and inexpensive vectors. In addition, they reproduce only in insect cells, and because they do not reproduce in mammalian cells, they improve their biological immunity. As a result of these beneficial properties, baculoviruses are an attractive option for gene transfer (Hu 2006; Schaly et al. 2021).

Baculovirus transcription and replication occur in three stages i.e., early, late, and very late steps. The initial phase begins with binding, genome entry, coating, and viral gene expression. The activation of these genes enables DNA synthesis and the production of late genes, which are mostly structural proteins. The connection between cell surface receptors and coating proteins, such as Gp64, causes the cell to stick to the virus. Then endocytosis occurs, and by changing the pH of the viral coat, it merges with the endosome membrane. This connection releases the nucleoside into the host cytoplasm and from there, it goes to the nucleus. Baculoviruses do not integrate into mammalian cells, making them a good option for in-vivo gene therapy, but several problems must be solved first including;

1. Baculoviruses do not spread in the injected tissue
2. They can be rapidly deactivated by the host's immune system (Hu 2006; Schaly et al. 2021).

To address these, a series of genetic engineering has been done, such as connecting the DAF factor, portin-A, which binds to C4B, on the baculo coat and renders them safe. Because baculoviruses can stimulate the immune system well, they can therefore be used as adjuvants in vaccines. Baculo is also used in the ex-vivo system, for example, bone marrow mesenchymal cells were transferred with Baculo vectors to rabbits with osteochondral disorders, which resulted in improvement (Hu 2006; Schaly et al. 2021).

After the discovery and understanding that baculoviruses were capable of transfecting mammalian cells, their therapeutic potential expanded rapidly. To express foreign genes, a viral or mammalian promoter must be identified. Due to the high activity of viral promoters such as p10 and polyhedrin, they are mostly used for transcription. A mammalian promoter called BacMam can also be used (Hu 2006; Schaly et al. 2021).

Today, one of the most widely used systems is the Bac-to-Bac system. This system consists of three antibiotics (ampicillin, kanamycin, and gentamicin) and an intermediary plasmid for introducing foreign genes through targeted transfection. By making changes in the genome of baculoviruses, they can be used. Cytosolic chaperones such as hsp70 and hsp40 prevent the aggregation of polypeptides, so their placement in the baculovirus genome increases the proper folding of proteins. The method of entering the host cells and producing viral proteins by the virus is essential for treatment (Hu 2006; Schaly et al. 2021).

One of the obstacles to viral gene therapy is the complexity of native proteins. A scientist named Berger and his colleagues combined a bunch of small synthetic DNA plasmids called acceptors and donors. Receptors can be loaded using multiple genes to produce eukaryotic protein complexes with multiple subunits, called MultiBac. The discovery of this system made it possible to understand and treat complex molecules that were previously unavailable. The expression of these multi-subunit proteins is essential for protein function and could provide a functional pathway for individualized therapy. One of the advantages of these multi-subunit proteins is that the large cloning capacity of baculoviruses allows the insertion of large genes. Baculoviruses can be used in vaccines and in the treatment of immune diseases, including influenza, SARS, HIV, Sudan, Ebola and Marburg viruses, rabbit hemorrhagic disease virus, sarcoma virus, and diabetes type 1 (Hu 2006; Schaly et al. 2021).

Herpes Virus

Herpes simplex virus (HSV) is a dsDNA virus having an envelope. This virus consists of several components, including a glycoprotein outer coat, an amorphous layer called the tegument, and an icosadeltahedral capsid. The life cycle of the virus begins with viral ligands attachment to the host cell. One way of HSV-1 enterance is through endocytosis. Virion integration into the plasma membrane is another method of virus entry into host cells that is independent of pH and requires several viral glycoproteins and cellular receptors (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020).

Herpes viruses are capable to enter a latent state and subsequently escape the host's immune system and cause persistant infction. Herpes viruses may cause complications with violent disease in immunocompromised individuals, however, the majority of the society experiences few complications from herpes virus infections. Herpes simplex virus type 1 infects certain cells, such as epithelial cells and neurons. They have suitable properties to be used as therapeutic agents including:

1. HSV shows a wide range of host cells and cellular receptors.
2. Herpes virus is very infectious.
3. Non-dividing cells are infected by HSV.
4. Recombinant HSV vectors of high purity can be easily produced.
5. The latency of the virus provides the long-term effects and their expression in neurons.
6. Due to the ability of HSV- 1 to pass through the blood-brain barrier, this virus can infect neurons, thus making it an effective vector for the treatment of neurological cancers.
7. HSV-1 can convey a large amount of episomal extra genetic material. At the same time, it avoids the risk of insertional mutagenesis potential, which is seen in some other vectors such as retroviruses or AAV (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020).

Currently, 9 herpes viruses may infect humans. These viruses are divided into three subgroups, alpha (α), beta (β), and gamma (γ), based on the speed of virus replication and the infected host cells (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020).

Human Herpesviruses

HSV-1 is a neurotropic virus that has significant and good adaptations to the nervous system and thus can be used for neurological problems. Various herpes vectors have been applied so far, but they have faced problems, which include:

(1) Suppression of viral lytic gene expression and innate immune system responses;

(2) Promoter design to achieve suitable and stable gene expression.

(3) Strategy to target a specific neuron;

(4) Simultaneous expression of various genes (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020).

Several HSV genes have been identified. By modifying these genes, they can be used as a means of gene transfer in therapy, but the question is, which genes should be changed in an HSV vector? Thymidine kinase (TK), ribonucleotide reductase (RR), virion host silent (VHS), and ICP34 are essential for virus function.

- TK is essential in optimizing nucleic acid metabolism and effective replication in neurons.
- RRs are essential for the synthesis of new viral genome.
- VHS causes instability in host RNAs
- ICP34.5 is essential for HSV virulence (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020).

A main challenge for herpes vector application is its latency. After establishing an infection in the body, HSV-1 lies dormant, and can even reactivate several times during a lifetime. Recombinant HSV vectors can be used to get rid of latent HSV. An HSV-1 vector that carries the interferon gamma (IFN-γ) gene causes the expression of the IFN gamma gene in peripheral neurons and thus disturbs the latent infection in peripheral neurons. The HSV-1 vector has also been studied for cancer treatment. There is great therapeutic potential based on HSV vectors to treat a wide range of cancers. Glioblastoma is a dangerous and aggressive type of brain cancer that cannot be completely cured with the current treatments (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020). Studies for the result and effectiveness of this method are ongoing.

Melanoma is one of the most common types of cancer, which include malignant melanocyte tumors that develop in the skin. HSV vectors have developed a way to kill melanoma cells when injected directly into lesions. This vector lacks the ICP34.5 and ICP47 genes, which enhance the host's antitumor response. Pancreatic cancer accounts for a small number of cancer-related deaths, but these cancers are difficult to treat, often diagnosed at late stages, and spread rapidly. A combination of oncolytic herpes viruses and chemotherapy can effectively treat pancreatic cancer. The oncolytic virus tested is HF10, which was created by the spontaneous mutation of a laboratory strain of HSV-1. This approach did not cause chronic complications (Manservigi et al. 2010; Mansouri and Berger 2018; Mody et al. 2020).

Vaccinia Virus

Vaccinia virus is an orthopoxvirus of the Poxviridae family that has a linear ds DNA. The smallpox virus was eradicated in 1980, but researches on the vaccinia virus are ongoing because the vaccinia virus, as a foreign gene expression vector, is a suitable model to study virus-host interactions (Jefferson et al. 2015; Haddad 2017; Yang et al. 2018). The vaccinia virus has certain advantages as a therapeutic vector including;

1. Its multiplication cycle is fast, and it has high transmission efficiency
2. Because the replication and transcription of the vaccinia virus is carried out in the cytoplasm, therefore, its genomic DNA cannot integrate into the host's chromosomes and isn’t carcinogenic.
3. Vaccinia virus can infect almost all types of tumor cells
4. They have the power to stimulate the host's immune system
5. Can be injected intravenously for more effective delivery
6. It was used to eradicate smallpox, and its side effects were very few.
7. It is stable (Jefferson et al. 2015; Haddad 2017; Yang et al. 2018)

The mechanism of the effect of the virus in tumor cells is such that the successive multiplication of the virus in tumor cells causes raw materials, energy, and reaction sites to be inhibited in the host cell and the result is the lysis of tumor cells. Furthermore, the vaccinia virus promotes tumor cell apoptosis. It infects the endothelial cells inside the tumor and causes apoptosis and disintegration of the tumor vessels. Four infectious forms of VACV develop during the life cycle of the virus. These forms are:

Intracellular mature virion (MV)
Intracellular enveloped virion (IEV)
Cell-associated enveloped virion (CEV)
Extracellular enveloped virion (EEV) (Jefferson et al. 2015; Haddad 2017; Yang et al. 2018).

Among the uses of these forms for gene therapy, the combination of viral therapy with cytokines has been done to destroy the tumor. One of its first attempts was to develop strains of the vaccinia virus that encoded GM-CSF, JX-549, and JX-963. The result of their test showed that anti-tumor immunity increases due to the expression of the GM-CSF gene at the site (Jefferson et al. 2015; Haddad 2017; Yang et al. 2018).

Another oncolytic potential was inhibition of tumor vasculature through expression of the endostatin/angiostatin fusion gene by targeting vascular endothelial growth factor (VEGF). Inhibition of VEGF has been widely studied in a number of cancer models, which led to a decrease of blood vessels in tumor tissue. This decrease in tumor vasculature was associated with the regression of tumors (Jefferson et al. 2015; Haddad 2017; Yang et al. 2018).

Conclusion

Current advances in the field of gene therapy have opened the way for the treatment of many diseases. The design and use of viral vectors, the management of gene therapy research protocols, the identification of risk levels and the development of acceptable policies for the risk assessment process have led to the use of these vectors as promising tools in gene therapy-based research.

REFERENCES

Abraham RT and Weiss A, 2004. Jurkat T cells and development of the T-cell receptor signalling paradigm. Nature Reviews Immunology 4(4): 301-308.

Escors D and Breckpot K, 2010. Lentiviral vectors in gene therapy: their current status and future potential. Archivum Immunologiae et Therapiae Experimentalis 58(2): 107-119.

Gowing G et al., 2017. Ex vivo gene therapy for the treatment of neurological disorders. Progress in Brain Research 230: 99-132.

Haddad D, 2017. Genetically engineered vaccinia viruses as agents for cancer treatment, imaging, and transgene delivery. Frontiers in Oncology 7: 96.

Hu YC, 2006. Baculovirus vectors for gene therapy. Advances in Virus Research. 68: 287-320.

Jefferson A et al., 2015. The mechanisms of genetically modified vaccinia viruses for the treatment of cancer. Critical Reviews in Oncology/hematology 95(3): 407-416.

Lee CS et al., 2017. Adenovirus-mediated gene delivery: potential applications for gene and cell-based therapies in the new era of personalized medicine. Genes and Diseases 4(2): 43-63.

Li C and Samulski RJ, 2020. Engineering adeno-associated virus vectors for gene therapy. Nature Reviews Genetics 21(4): 255-272.

Manservigi R et al., 2010. HSV recombinant vectors for gene therapy. The Open Virology Journal 4: 123.

Mansouri M and Berger P, 2018. Baculovirus for gene delivery to mammalian cells: Past, present and future. Plasmid 98: 1-7.

Merten OW et al., 2016. Production of lentiviral vectors. Molecular Therapy-Methods and Clinical Development 3: 16017.

Mody PH et al., 2020. Herpes simplex virus: A versatile tool for insights into evolution, gene delivery, and tumor immunotherapy. Virology: Research and Treatment 11: 1178122.

Schaly S et al., 2021. Baculoviruses in gene therapy and personalized medicine. Biologics: Targets and Therapy 15: 115.

St George JA, 2003. Gene therapy progress and prospects: adenoviral vectors. Gene Therapy 10(14): 1135-1141.

Tomás HA et al., 2013. Lentiviral gene therapy vectors: challenges and future directions. IntechOpen 2013: 27.

Wang D et al., 2019. Adeno-associated virus vector as a platform for gene therapy delivery. Nature Reviews Drug Discovery 18(5): 358-378.

Yamamoto Y et al., 2017. Recent advances in genetic modification of adenovirus vectors for cancer treatment. Cancer Science 108(5): 831-837.

Yang X et al., 2018. Progress in gene therapy using oncolytic vaccinia virus as vectors. Journal of Cancer Research and Clinical Oncology 144(12): 2433-2440.

Zhao Z et al., 2022. Viral vector-based gene therapies in the clinic. Bioengineering and Translational Medicine 7(1): e10258.

29

Social Awareness, the Main Dare for Environmental Health

AUTHORS DETAIL

Miguel Ángel Karam Calderón[1], Shadye Matar Khalil[2], Gauddy Lizeth Manzanares-Leal[1], Yazmín Castillo Sánchez[1], Pablo Antonio Moreno-Pérez[1], Ninfa Ramírez-Durán[1*]

[1] Facultad de Medicina, Universidad Autónoma del Estado de México, Toluca, Estado de México.
[2] UNAD, Florida, United States of America.
*Corresponding author: ninfard@hotmail.com

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INTRODUCTION

One of the biggest problems that is caused by human beings on this planet is undoubtedly the damage to nature, damage that affects them, but they do not seem to be aware of it because their predatory behavior continues to damage their environment, and it seems that there are no mechanisms to stop such behavior. The current situation of damage to the environment originates from the predatory attitude of human beings and their ambition for money, factors that are fully linked (Graham and White 2016).

However, at other times there was a very different behavior. A very special conscience about the care of the environment could be seen in the actions of Nezahualcoyotl, king of Texcoco, Mexico. He implemented in his time a series of measures to protect the environment, such as the development of forests, dams to prevent salt and fresh water from mixing, botanical gardens, and an aqueduct to provide water to the great Tenochtitlan.

Likewise, in the Middle East, since the Middle Ages, activities were carried out that aimed to make people environmentally conscious, and treaties were written about air, water, and soil pollution, inadequate management of solid waste, and environmental evolutions of localities (Gibson and Farah 2012; Yeatts et al. 2012).

However, over time this has been left aside. Human beings seem immersed in a state of unconsciousness that does not allow them to realize the damage they are causing to the environment and the consequences for their environment and themselves. Human beings have lost themselves in such a state of unconsciousness that they are only interested in possessing and possessing more and more, regardless of what this may mean. They damage forests, rivers, air, water, and food and even when we are already suffering the consequences, as evidenced by droughts in some parts of the world or floods in others, the human being is still not fully aware of this and continues to be a voracious predator. The environmental deterioration we are currently experiencing increases the demands that the world's population recovers its state of consciousness. It is necessary to analyze that relating to nature and oneself is not the correct one, and a change in people's compartments is essential; otherwise, there will be adverse consequences on people's health (Zinsstag et al. 2018; Rodríguez-Cruz and Niles 2021).

Factors Affecting Climate Change

Climate change is currently the main environmental problem and one of the most significant challenges of our time, where no country is immune to its effects, which are already having repercussions in various areas such as the economy, health, security, politics, and food production (Butler 2018).

Climate change refers to long-term changes in temperatures and weather patterns. These changes can be natural, for example, through variations in the solar cycle. But since the 19th century, human activities have been the main driver of climate change, mainly due to burning fossil fuels such as coal, oil, and gas. Burning fossil fuels generates greenhouse gas emissions that act as a blanket around the Earth, trapping the sun's heat and raising temperatures. From the so-called Industrial Revolution to today, industrial processes have been developed by burning fossil fuels (oil, gas and their derivatives, such as gasoline) and taking undue advantage of natural resources. (Oreskes 2004).

Carbon dioxide and methane are examples of greenhouse gas emissions that cause climate change. These gasses come from using gasoline to drive a car or coal to heat a building. Land and forest clearing can also release carbon dioxide. Landfills are a significant source of methane emissions. Energy, industry, transportation, buildings, agriculture, and land use are among the main emitters (Gavurova 2021; Li et al. 2022).

Current evidence attributes the global warming observed since the mid-20th century to the action of several greenhouse gases produced by anthropogenic activities (Warrach 2001). Increasingly, human activities significantly influence changes in the natural greenhouse effect because burning coal and oil combines carbon with oxygen in the air to form CO2. To a lesser extent, deforestation for agricultural purposes, industry, and other human activities has increased the concentration of greenhouse gases (Oreskes 2004; Alam and Starr 2009; Galford et al. 2010).

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According to the Intergovernmental Panel on Climate Change (Solomon et al. 2007), a group of 1,300 independent scientific experts from around the world under the auspices of the United Nations concluded that there is a greater than 95% probability that in the last 50 years, human activities have warmed our planet. About 150 years since the Industrial Revolution, our civilization has been increasingly dependent on this activity, which has significantly increased carbon dioxide levels in the atmosphere from 280 to 400 parts per million (Solomon et al. 2007).

It is often thought that climate change means an increase in temperature. However, this is not that simple, as the Earth is a system where everything is connected, and changes in one area can influence others. The consequences of climate change now include various situations we are already experiencing, particularly in European and Asian countries, such as intense droughts, water shortages, severe fires, rising sea levels, floods, melting of the poles, catastrophic storms, and declining biodiversity.

Together, the consumption style of the current political-economic model, a scheme based on "having" as a synonym for "being successful in life," does not have in mind the overcoming of hunger and the needs of the low-income population but rather the accumulation of capital and its apparent benefits, tends to ignore the increase in the number of poor people, the pollution and degradation of resources and habitat, as well as the effects of its actions on climate change. This model's observable consequences openly question the current development scheme's production and consumption style as we move towards horizons that endanger life on our planet. This situation has highlighted the urgent need to undertake further development, a development based on the rational use of natural and social resources, which promotes sustainable production, equitable consumption, and the use of technologies that limit human effects on nature and climate. It is necessary to change the state of consciousness of human beings, allowing them to perform actions that reflect their rational capacity (Anderson 2011).

In an increasingly complex and interconnected world, with a genuine and existential threat such as climate change, there is a growing call to conscience to allow individuals, as agents of change, to recover, mainly the values and attitudes that make us human (Raducu 2020).

Climate Change and Poverty

Climate change can affect our health, ability to grow food, housing, security, and work. Several studies have shown that more and more people are vulnerable to climate impacts, particularly the poor (Levy and Patz 2015; Butler 2018; Jessel et al. 2019; Fahad and Wang 2020; Raducu 2020). For more than a decade, there has been a consensus that development is influenced by climate change (Anderson 2011). Climate change and economic, social, and health crises are closely linked and lead to rethinking how we analyze and face these crises. Initially, we must avoid human-nature dualism and rethink ourselves as complementary (Molina-Vargas 2021).

Climate change negatively affects living conditions and health, both mentally and physically. It also affects gender disparities, the standard of living, education, inequality, and poverty. The adverse and disproportionate effects of climate events and natural disasters originate or exacerbate inequality in vulnerable populations, pushing them into poverty or extreme poverty, so it is essential to lessen the negative effect among them (Busso and Messina 2020).

The impact of natural disasters and climate change (floods, droughts, heat waves) on vulnerable populations is invisible to the global economy. The link between climate vulnerability and poverty goes both ways; firstly, the environment and climate can push people directly or indirectly into poverty, which would affect the environment (Hallegatte et al. 2018) and secondly, a link to consider global climate change mitigation policies. Various authors (Yohe and Tol 2002, Nicholls and Tol 2009; Hope 2006; Mendelsohn et al., 2006; Hallegatte et al. 2018) expose that the distribution of climate impacts is heterogeneous, where the use of the world Gross Domestic Product GDP to measure the climate cost can disproportionately hide the significant impacts between countries and specifically in developing countries and regions.

Climate Change and Social Awareness

Although concern for the environment is not a new issue, there has been a long-standing debate on the economic, socio-cultural, and political models prevailing worldwide, and various forums have been held with the participation of almost all countries, which are so-called Environmental Summits, with meager results (Flandoli and Romero-Riaño 2020). In recent years, the "environmental conscience" has increased. It is a philosophy of life concerned about the environment and protecting it to preserve it and ensure its present and future balance, recognizing the impact of human behavior on natural resources, and rethinking ourselves as the most devastating species for the planet since without it we could not exist and much less evolved. In contrast, Earth's planet can exist and resurface without the human species; this implies recognizing the impact of human behavior on natural resources and rethinking ourselves as the most devastating species for the planet. At this point, it is essential to recognize that humans would not be able to exist without planet earth, but conversely, the planet can persist without human presence.

The planet earth is a space shared by millions of diverse species that inhabit the different ecosystems of our planet, such as seas, rivers, forests, and jungles. However, little consideration is given to the existence of all these forms of life, both animal and plant, and if it is considered, a form of economic exploitation is sought without maintaining a scheme of sustainability. Environmental awareness must be an integral part of human beings. It must be a conscience that allows him to enjoy well-being, where self-care and care for others and the environment can be carried out, and various ethical aspects are involved. Since values are increasingly scarce, human beings have been devalued and still devaluing their lives and lives in general (Laso et al. 2017).

Modern systems have generated an imbalance in the human-environment balance, causing negative impacts not only on physical and mental health but also on spiritual health (García 2013; Jones et al. 2018; Matar and Ortiz 2021). Therefore, it is valid to consider elements, not only of biological character but even of a spiritual type, in environmental awareness. There is a need to recover the consciousness of human being that allows it to understand the processes of nature and respect them, to live and coexist with its fellows and with the entire environment that surrounds it, and live in harmony and peace (Koehrsen 2018; Ramli 2022).

Indigenous wisdom has a cosmovision, wisdom, and practices where respect and harmonious coexistence with mother earth prevail. Indigenous worldviews are transmissible and shape the relationship between these peoples, the environment, and the people who inhabit it. In this sense, the relationship with the environment is not superficial but profound in providing resources, protection, and health (Rai and Khawas 2019). For thousands of years, native cultures have extracted from nature everything they need to live in a wise relationship of balance that has kept them aware that they are not owners but members of their environment. Their cultural diversity has merged and enriched with biological diversity to form their biocultural heritage in this worldview. However, the projects of state building and modernization, through a Western worldview, have discredited this knowledge, reconfiguring the relationship with nature as a force to be subdued. Recognizing and being aware of our close links with nature would facilitate changes in cultural perspective in favor of the environment. It is necessary to merge scientific knowledge with ancestral knowledge to promote the reconciliation of this link (Rai and Khawas 2019; Ali et al. 2021).

Indigenous peoples and megadiversity are two elements that have made possible the appropriation of the biological diversity in Mexico, which represents 10% of the species that exist in the world and generated a bio-culture that enriched the food source, the world can enjoy today. However, the vision that during the last 30 years only sought to increase food production at an industrial level, at the expense of nature and ecosystems. The result is the wear and tear of the land by forcing the change of land use to move from a forest or vegetable system to a monoculture agricultural system or extensive cattle ranching and the natural exchange between animal and vegetable species that for centuries was used by indigenous cultures was interrupted (Mendelsohn 2009).

Undeniably, the oblivion of traditional practices developed in harmony with the times of nature that have been broken with their due consequences. Hence, it is necessary to preserve and disseminate our wisdom from our ancestors, which is based on the deep knowledge of nature and its cycles, and therefore have a deep respect for it and love it. This action will create awareness about the urgent need to protect and conserve the environment. It will strengthen the actions that will allow us to recover the human conscience that we are a whole, fully linked to our environment, so it is necessary to recover the absolute respect for Mother Earth in a relationship that allows us to understand that we are not the "owners" of nature, but that "we are part of it" (Paneque-Gálvez 2018; Molnár and Babai 2021).

Environmental awareness, therefore, must go beyond the mere teaching of a few classes in school. Teaching how to recycle requires environmental literacy strategies for all ages and contexts and allowing people to have knowledge of the environmental reality and identify its problems, understanding social, historical, and ecological processes. The development of environmental sensitivity and the search for solutions and available means of action, with which a culture of environmental values can be developed since environmental care is not only the task of ministries and international institutions designed for this purpose. It is necessary to think, act sustainably, and work intersectionally with all the people who make up societies (Turaga et al. 2010; Jena 2018).

Environmental awareness is the certainty that natural resources must be cared for, protected, and used responsibly and rationally to provide well-being to the planet we inhabit. It is also considered a philosophy of life that cares about the environment and protects it to conserve it and thus guarantee its balance in the present and future (Rodriguez-Ibeas 2007).

It is urgent to recover social cohesion because of an economic-political system that has favored individualism and has fragmented us as a human society. Obvious evidence has been how the Covid-19 pandemic has shown us the attitudes of selfishness and lack of equity for its control to such an extent that we have been more than two years, and despite the support with vaccines, it has not been possible to control this pandemic. Therefore, it is necessary to recover the solidarity among people that leads us to understand that we only have this planet and that most resources, besides being limited, are not renewable (Uzzel et al. 2002).

The global environmental crisis with anthropogenic roots is a current threat that must be faced. It concerns governments, companies, and society in general, so an economic, social, and environmental transformation is imperative for an integral development not only of society but of the planet itself. In that sense, environmental awareness must promote a change that generates social, emotional, and economic welfare (Kaufmann et al., 2017).

Significant challenges require developing and potentiating environmental awareness since it is complex to find shared values to mobilize consciences and guide individual and collective actions in a globalized and open world. That is why they suggest that to address environmental problems; it is required to address them as a moral problem, to penetrate values to build a universal and inclusive identity in the face of structural and existentialist crises and, thus, achieve environmental peace in countries and between countries (Moyano 2018).

On June 5, 2022, the theme of World Environment Day, considered a motto of "One Earth," aims to establish sustainable actions that allow human beings to safeguard natural resources and promote social responsibility. So far, the social sensitivity facing the course of the socio-environmental eventualities has been minimal in reversing the crisis of values that we have socially embraced for more than 50 years. There has been a notorious lack of commitment and respect for environmental conservation and overcoming social resistance to build a sustainable and harmonious model between nature and human beings (Kovel 2021).

Conclusion

The current times, shaken by a pandemic, growing poverty, and climate change, demand the recovery of conscience among individuals, societies, and governments. The generation of an environmental conscience as the basis of all human behavior cannot be postponed. It is necessary learning regardless of our age or our knowledge, a philosophy of life that cares about the environment and protects it to preserve it and ensure its present and future balance, that cares about life itself and takes care of it. It is a moment that demands that people react and move from a submissive attitude to a critical attitude that leads to a "liberating conscience." It requires a conscience based on values that allow us to have a conviction that determines conduct or behavior of respect and understanding between human beings and their environment and allows us to understand that we are part of this nature.

REFERENCES

Alam SA and Starr M, 2009. Deforestation and greenhouse gas emissions associated with fuelwood consumption of the brick making industry in Sudan. The Science of the Total Environment 407: 847–852.

Ali T et al., 2021. Facilitating Sustainable Disaster Risk Reduction in Indigenous Communities: Reviving Indigenous Worldviews, Knowledge, and Practices through Two-Way Partnering. International Journal of Environmental Research and Public Health 18: 855.

Anderson S, 2011. Climate change and poverty reduction. 1st Ed., International Institute for Environment and Development (IIED), London (United Kingdom).

Busso M and Messina J, 2020. The inequality crisis: Latin America and the Caribbean at the Crossroads. Inter-American Development Bank 32: 0002629.

Butler CD, 2018. Climate Change, Health, and Existential Risks to Civilization: A Comprehensive Review (1989^{-}2013). International Journal of Environmental Research and Public Health 15: 2266.

Kaufmann RK et al., 2017. Spatial heterogeneity of climate change as an experiential basis for skepticism. Proceedings of the National Academy of Sciences, 3 Jan 2017, pp: 67-71.

Fahad S and Wang J, 2020. Climate change, vulnerability, and its impacts in rural Pakistan: a review. Environmental Science and Pollution Research International 27: 1334–1338.

Flandoli AM and Romero-Riaño E, 2020. The role of gamification in the environmental awareness: a bibliometric review intellectual structure evolution. Prisma Social 30: 161-185.

Galford GL et al., 2010. Greenhouse gas emissions from alternative futures of deforestation and agricultural management in the southern Amazon. Proceedings of the National Academy of Sciences of the United States of America, 16 Nov 2010, pp: 19649–19654.

García J, 2013. Considerations on Natural and Traditional Medicine, the scientific method and the Cuban health system. Revista Cubana de Salud Pública 39: 540-555.

Gavurova B et al., 2021. Greenhouse Gas Emissions and Health in the Countries of the European Union. Frontiers in Public Health 9: 756652.

Gibson JM and Farah ZS, 2012. Environmental risks to public health in the United Arab Emirates: a quantitative assessment and strategic plan. Environmental Health Perspectives 120: 681–686.

Graham H and White PC, 2016. Social determinants and lifestyles: integrating environmental and public health perspectives. Public Health 141: 270–278.

Hallegatte et al., 2018. Poverty and climate change: introduction. Environment and Development Economics 23: 217-233.

Hope CW., 2006. The marginal impact of CO2 from PAGE2002: an integrated assessment model incorporating the IPCC's five reasons for concern. Integrated Assessment Journal 6: 19-56.

Jena AK, 2018. Effects of Community Sanitation Program on the Awareness of Environmental Sustainability in Assam, India. International Quarterly of Community Health Education 39: 51–61.

Jessel S et al., 2019. Energy, Poverty, and Health in Climate Change: A Comprehensive Review of an Emerging Literature. Frontiers in Public Health 7: 357.

Jones MJ et al., 2018. Principles and challenges of applying epigenetic epidemiology to psychology. Annual Review of Psychology 69: 459–485.

Koehrsen J, 2018. Eco-spirituality in environmental action: studying dark green religion in the German energy transition. Journal for the Study of Religion, Nature and Culture 12: 34-54.

Kovel J, 2021. The enemy of nature: The end of capitalism or the end of the world? In Power and Inequality, 2nd Ed., Routledge.

Laso SS et al., 2017. Environmental Awareness as a Mediator Variable on Conceptions of Science Teaching and Learning. International Journal of Environmental and Science Education 12: 1401-1426.

Levy BS and Patz JA, 2015. Climate Change, Human Rights, and Social Justice. Annals of Global Health 81: 310–322.

Li M et al., 2022. Human metabolic emissions of carbon dioxide and methane and their implications for carbon emissions. The Science of the Total Environment 833: 155241.

Matar SH and Ortiz M, 2021. A holistic health perspective as a principle for understanding mental health. Centro de investigación y acción psicosocial comunitaria: un escenario para la construcción de paz. Libros Universidad Nacional Abierta y a Distancia.

Mendelsohn R, 2006. The distributional impact of climate change on rich and poor countries. Environment and Development Economics 11: 159–178

Mendelsohn R, 2009. The impact of climate change on agriculture in developing countries. Journal of Natural Resources Policy Research 1: 5-19.

Molina-Vargas RM, 2021. Climate change and inequalities; the need to reanalyze crises from the world-ecology. Journal of Latin American Sciences and Culture 3: 4

Molnár Z and Babai D, 2021. Inviting ecologists to delve deeper into traditional ecological knowledge. Trends in Ecology and Evolution 36(8): 679–690.

Moyano EE, 2018. An essay on Laudato si' and its contribution to environmental awareness. Revista de Fomento Social 441–456.

Nicholls RJ and Tol RSJ, 2006. Impacts and responses to sea level rise: a global analysis of the SRES scenarios over the twenty-first century Philosophical Transactions of the Royal Society 364: 1073–95.

Oreskes N, 2004. The Scientific Consensus on Climate Change. Science 306: 1686.

Paneque-Gálvez J et al., 2018. High overlap between traditional ecological knowledge and forest conservation found in the Bolivian Amazon. Ambio 2018: 908-923.

Raducu R et al., 2020. Climate Change and Social Campaigns. Journal of Medicine and Life 13: 454–457.

Ramli S, 2022. Green Spirituality: The Effect of Spirituality Attitude for Students' Environment Care Character. JPI (Jurnal Pendidikan Indonesia) 11: 2.

Rai P and Khawas V, 2019. Traditional knowledge system in disaster risk reduction: Exploration, acknowledgement and proposition. Jamba (Potchefstroom, South Africa) 11: 484.

Rodríguez-Cruz LA and Niles MT, 2021. Awareness of climate change's impacts and motivation to adapt are not enough to drive action: A look of Puerto Rican farmers after Hurricane Maria. PloS One 16: e0244512.

Rodriguez-Ibeas R, 2007. Environmental product differentiation and environmental awareness. Environmental and Resource Economics 36: 237-254.

Solomon S et al., 2007. Summary for policymakers. Climate change 1-18.

Turaga RM et al., 2010). Pro-environmental behavior: rational choice meets moral motivation. Annals of the New York Academy of Sciences 1185: 211–224.

Uzzell D et al., 2002. Place identification, social cohesion, and enviornmental sustainability. Environment and Behavior 34: 26-53.

Warrach K et al., 2001. Treatment of frozen soil and snow cover in the land surface model SEWAB. Theoretical and Applied Climatology 69: 23–37

Yeatts KB et al., 2012. Conducting environmental health research in the Arabian Middle East: lessons learned and opportunities. Environmental Health Perspectives 120: 632–636.

Yohe G and Tol R, 2002. Indicators for social and economic coping capacity—moving toward a working definition of adaptive capacity. Global Environmental Change 12: 25–40

Zinsstag J et al., 2018. Climate change and One Health. FEMS Microbiology Letters 365: 85.

30

Emerging Infectious Diseases in Perspective to Climatic Conditions

AUTHORS DETAIL

Muhammad Bilal, Muhammad Kashif Saleemi, Aisha Khatoon, Muhammad Imran Arshad, Muhammad Imran and Shafia Tehseen Gul*

[1]Department of Pathology, University of Agriculture, Faisalabad-Pakistan
[2]Institute of Microbiology, Faculty of Veterinary Science, University of Agriculture, Faisalabad-Pakistan
*Corresponding author: drshafia66@yahoo.com: dr.shafia.gul@uaf.edu.pk

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INTRODUCTION

As per the statement of The World Health Organization (WHO), mankind facing greatest threats in twenty-first century are "climate change and global warming." Posing serious threats to human life and other creatures on the planet earth (WHO 2017). Despite the fact that global warming is one of the many features involved with climate change, the terms "climate change" and "global warming" are frequently used interchangeably. When someone uses the term "global warming," that typically describes the observed increase in normal global temperature over past few years, both in terms of incidence and intensity (Myhre et al. 2019). It is mainly due to the green house effects due to the increased fossil fuel consumption alongwith deforestation mean cutting of trees and forests for the human uses. This rise in temperature is higher near the poles and less close to the equator. According to computer simulation models, it might range between 1.6 to 6°C increase per year and is expected to accelerate in the coming years (Ghazali et al. 2018).

Infectious disease epidemiology changes are connected to global warming and mainly linked with changing habitats, population susceptibility, and greater exposure to etiological agent. These different factors contribute to the higher prevalence of diseases, including both emerging and re-merging infections mostly and more quickly the transboundary diseases (TBDs) and emerging infectious diseases (EIDs) (Khansins et al. 2005; Baker et al. 2022). The geographic distribution of vectors and intermediate hosts, such as rodents, migratory birds, and invertebrate hosts (insects), has also been affected due to global warming (El-Sayed and Kamel 2020). Recently, the WHO has estimated that zoonotic bacterium pathogen i.e., *Chlamydia*, which can be spread by the close connection with parrots, affects more than 90 million people in a single year (WHO 2017). The sickness is connected to bird migration and mobility, which has strong association with the ecological and climatic changes (Nava et al. 2017). Contrarily, "climate change" denotes to long-term, computable variations in the climate that have been observed. Extreme weather events, such as droughts, heat waves, wildfires, tropical cyclones, gradual melting of glaciers, loss of river deltas and towns near the coastal areas, extreme rainfall and flooding, and dust storms are all indicative of the climatic change, in addition to other important changes including the unnecessary cutting of trees and use of massive bushmeat are also responsible for the emerging of infectious diseases (Weilnhammer et al. 2019).

The harm to the human health due to the climate change and global warming is underrated yet. According to estimates, changes in environmental factors are responsible for 36% of all infant and young child mortality around the globe and 34% of total childhood illnesses. Climate change and different environmental factors have a significant impact on outbreaks of majority of newly emerging diseases such as dengue fever, cholera, deadly malaria, diarrhea, and many other diseases (Mutlu and Nacaroglu 2019). Climate change can also affect human socio-demographics and cause a mass emigration of people and domestic animals from dry, hot regions to the places with better living conditions (El-Sayed and Kamel 2020). Along with this, there are global alterations to the traditional geographic circulation of wildlife, insects, and rodents (Buhler et al. 2022). Climate change, ecosystem disruption, exposure to vector insects, and the spread of infectious diseases have a known epidemiological linkage (Goshua et al. 2021). Better understanding of these connections makes it possible to forecast, how upcoming climate changes would affect the ecology of infectious agents, the transmission of infections, vectors (intermediate hosts), reservoir animals, and final hosts etc. (Sellers et al. 2019).

The melting of an ice layer that has been present for thousands of years is one of the most serious underrated effects of global warming in addition to causing several cities and river deltas to vanish from earth. The melting of the ice sheet will unfortunately also reveal other hidden biological components that have been buried under snow in addition to the mammoth carcasses that have been buried for thousands of years. As the year 2012, had witnessed the discovery of an ancient pathogen Virola virus in preserved mummy in Siberia which was 300 years old (Biagini et al. 2015). NASA investigators were also able to resuscitate bacteria that had been frozen in Alaska, thousands of years ago. Other researchers were able to separate the microorganisms from

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some ancient part of the world like Antarctica and still the story is continued (El-Sayed and Kamel 2020). Additionally, it was possible to identify live bacteria from a 25,000-year-old ice sample and Dominican amber (Josefsen et al. 2018). Over 75 years ago, the spores were buried beneath frozen soil, but now they are emerging as the ice melts. Among bacterial pathogens a classical example includes *Bacillus anthracis*, which is a spore-forming bacterium and lead to deadly diseases in warm blooded animals including humans known as “Anthrax”. The spores have a high level of environmental resistance and can remain active in a dormant state for 100 years. Floods and insects are two ways that may cause the spread of spores (e.g., tabanid flies). Using the same logic, it is also possible that smallpox virus may be kept in human leftovers buried in frozen soil (Ogden and Lindsay 2016).

On the health and wellbeing of people and animals, the climatic change has both direct and indirect effects. The increased frequency and length of heat waves have physical and psychological repercussions that might cause stress, pulmonary and circulatory impairment, heat strokes, and squamous-cell carcinomas over the long run. The drastic effects of different calamities like floods have also been observed on the wildlife population. The quantity, survival, and dispersion of diseases and their vectors are all directly impacted by global warming. Famines and the detrimental consequences of large-scale human/animal population migration waves are among the indirect repercussions (Joshi et al. 2020). According to an optimistic scenario, the ensuing ecological shift is expected to result in at least 250,000 more deaths per year between 2030 to 2050. Of these, 48,000 are anticipated to pass away through diarrhea, 60,000 from malaria, and the remaining 28,000 from starvation and heat exhaustion. Unfortunately, despite being the less responsible for CO_2 emissions and the greenhouse effect, poor developing nations are the most susceptible to these climatic effcets (El-Sayed and Kamel 2020).

Keeping in view the zoonosis of animal origin, more than 60% of infectious diseases appeared during 1940 to 2004 affecting humans are of serious concern in terms of public health. It has been documented that six (06) out of every ten (10) human infections are of animal origin and among these many of the diseases are emerging or remerging in the near past and their prevalence is increasing with every passing day. The world economy and public health are both greatly impacted by these outbreaks. Overall, 71.8% among these zoonotic diseases were caused by wildlife, and 22.8% were arthropod-borne illnesses (Zhang et al. 2019). It was surprising that Nepal developed endemic cases of numerous serious diseases which need some vectors for the transmission of diseases like Malaria, filariasis and Japanese encephalitis (Medone et al. 2015).

Emerging Infectious Diseases (EIDs)

Infectious diseases those become more prevalent or dangerous over the time are referred to as emerging infectious diseases (EIDs). The specific features of the EIDs includes (1) newly discovered, previously undiagnosed diseases and (2) long-standing diseases that have evolved or mutated from recognized agents to acquire novel traits (i.e., adaptation to new hosts or target population, new geo-graphic distribution, new clinical picture, new epidemiological profile, new spread pattern, or resistance to used therapeutics). The examples of EIDs in modern days are CCHF, Tuberculosis, brucellosis, and more resistant *E. coli* infection. In addition to this some drug resistant strains of the *E. coli* are also considered to be emerged (Mor et al. 2018).

Ebola virus (Africa), Middle East respiratory syndrome coronavirus (Middle East), Zika virus, chikungunya virus, yellow fever virus, and dengue virus (North and South America) were the main infectious agents that emerged and re-emerged in the past ten years (Antonenko et al. 2013). At least 50 new and reoccurred diseases were listed by the CDC. The diseases are broadly classified into human, animals and both human-animal’s communicable diseases termed as zoonotic diseases, the human disease which are emerged and remerged in the present and near past, tuberculosis, hemimorphic colitis, COVID-19, SARS, Malaria, and dengue fever. In case of animals the list of different disease includes *Pasteurella multocida*, Lumpy skin disease (LSD), trypanosomiasis, fascioliasis and zoonotic disease including MRSA, brucellosis, anthrax, avian influenza, rabies, babesiosis, giardiasis and leishmaniasis (Zhang et al. 2017). Social impact of climate change on livelihood, human society and infectious diseases is sown in Fig. 1.

However, it was shown that not all vectors are affected equally by climate fluctuations. For example, the geographic spread of mosquitoes is influenced by factors such as relative humidity, wind speed and direction, and rain that falls in the opposite direction from ticks. This is due to the mosquito life cycle, which depends on stagnant water for egg laying and larval stage development. In Asia and Africa, reports on the rise in malaria prevalence due to climatic changes have already been released (Andreassen et al. 2012). The aquatic ecology also exhibits the infiltration of novel parasites and their appearance in uninhabited places. At least 182 non-native parasite species have been found invading Canada's Laurentian Great Lakes area, meaning a new invader species appears once in every 4 months (Bojko et al. 2021). Coral reefs began to die as a result of severe diseases brought on by the rise in seawater temperature. For several fish species, coral reefs were the source of both a haven and food. The amount of diffused oxygen in the water likewise decreases as water temperature rises. All these elements cause a lot of disruption in the aquatic ecology which in returns possess a great threat not only to the human health but also to the economies along with many trade restrictions (Belter et al. 2020; Brugueras et al. 2020).

Neglected Tropical Diseases (NTDs)

In contrast to EIDs, another nomenclature of the diseases “Neglected Tropical Diseases" is also in use. Most of the diseases on the published database are known as neglected tropical diseases (NTDs). A category of bacterial, viral,

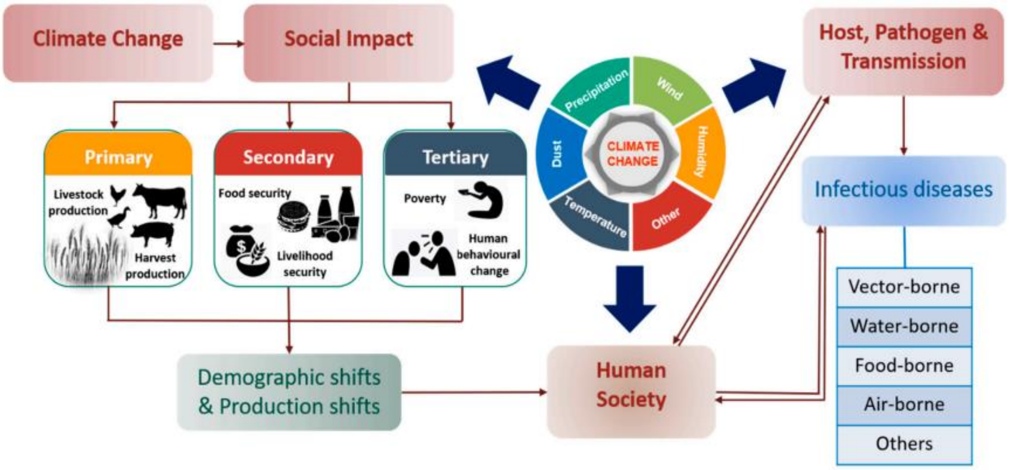

Fig. 1: Social impact of climate change affecting livelihood, human society and infectious diseases (Khan et al. 2019)

parasitic, and fungal infections known as NTDs are typically endemic to developing nations. Until such diseases started to spread and pose a significant threat to the civilized economies, the pharmaceutics industries did not spend enough money to find a cure for them because they were restricted to the developing nations, only (Huürlimann et al. 2011).

More precisely, the neglected tropical diseases are such diseases which historically possess no attention or given very less attention as compared to the other diseases. The influx of asylum-seeking refugees and illegal immigrants from nations suffering from war and famine in recent years has raised the prevalence of numerous NTDs or speed up their emergence in western nations (Liu et al. 2019). The human scabies infection caused by *Sarcoptes scabiei* mites is among the greatest instances. Despite having a global spread, the parasitic disease had a very low frequency in Europe. In the past ten years, outbreaks of scabies have been seen in Europe, including UK nursing home for elderly population (Ariza et al. 2013; Cassell et al. 2018).

NTDs are extremely susceptible to climate factors, which regulate their pattern of expansion. For instance, floods, heavy rain, rising temperatures, and increased humidity all contribute to survival of parasites at different infected stages (larva/metacercaria), which ultimately raises the occurrence of disease.There are five trematode species in the genus *Schistosoma* that need snails as intermediate hosts, including those that cause schistosomiasis, swimmer's itch and bilharzia. The parasite enters the body of host through skin (Wu et al. 2014; CDC 2017). Such disease with higher prevalence has also been reported from the different regions of the world including Europe (Morgan et al. 2021). One of the common worm parasites from the sheep and goats is *Fasciola hepatica* which is ignored but causes the illness in ovine and bovines because these are mainly grazing species and spend hours in grazing fields. It has also been categorized as zoonotic disease. The climate change and global warming may favor the growth of such domestic pathogenic parasites (Agache et al. 2022).

Along with the parasitic diseases already mentioned, this list of NTDs also includes many viral diseases including the following: (1) Rabies, a lethal and unnoted NTDs, is one of the most difficult diseases to control due to the freedom of the movement of wild animals (El-Sayed and Kamel 2020) (2) Dengue Fever, another most important and crucial disease, which causes 96 million new infections each year worldwide and is transmitted by mosquitoes. Only 500,000 of them get severe symptoms, resulting in 1250 causalities across the globe (Dhar-Chowdhury et al. 2017). (3) Marburg fever and highly associated Ebola hemorrhagic fever, both zoonotic viral infections are deadly and have connections with the environmental variations, particularly the seasonal patterns of rainfall and aridity. Consequently, it is expected that climate changes have impacts on the illness and global distribution of the viral diseases (Dhimal et al. 2015). In addition to parasitic and viral diseases, the leprosy may be among the most dangerous newly emerging bacterial NTDs. The pathogen responsible is *Mycobacterium lepra*. Even though leprosy has already been eradicated from Europe for centuries, some European countries have recently seen a partial resurgence of NTDs. In Spain, 168 leprosy cases were reported between 2003-2013. 40 of them were Spanish patients, with the remaining being undocumented immigrants (Sabourin et al. 2018).

Factors Contributing towards Outbreaks in Perspective to Climate Change

There are many factors responsible for the outbreaks of zoonotic infectious diseases. Source of disease transmission is one of the major contributing factors, so it has been discussed in detail here.

Food and Water Borne Diseases

Food- and water-borne illnesses pose a severe threat to global public health. Food and waterborne outbreaks are directly linked to climatic changes and ecosystem disruptions. These are more prevalent in the summer and become more prevalent as the temperature and humidity rises (Kumar et al. 2022). The frequency and intensity of floods and high rains has been increased due to ocean warming and hurricanes. Due to this the water-borne illnesses such as cryptosporidiosis, giardiasis, outbreaks with pathogenic *E coli*, *Shigella*, cholera, *Salmonella*, and viral hepatitis has also been increased (Pal et al. 2018). This is might be due the reason that floods and a rise in water level has affected the sewage drainage systems due to overloading and overflowing which ultimately becomes a source of contamination of drinking water and spreading of such infections among the human and animal population consuming that contaminated water (Portier et al. 2017).

Hence, the prevalence of the enteric/diarrheal illness has been increased manifolds around the globe and will continue to increase in coming years. In addition to these, global warming can also generate fatal epidemics, such as those brought on by the fatal thermophilic free-living amoeba *Naegleria fowleri*, which causes meningoencephalitis (Daisy 2019). The literature suggested that most water-borne outbreaks in the USA began during periods of heavy rainfall (Pal et al. 2018). Cholera, an illness brought on by *Vibrio cholerae*, is the most well-known water-borne illness. The disease is spread by consuming contaminated water. Cholera is a temperature-dependent illness that gets worse as the temperature of the water rises. *Vibrio spp.* infections are a classical illustration of how ecology and global warming affect the emergence of diseases. The number of plankton in the sea is impacted by the rise in water temperature. Vibrio population growth is caused by the symbiotic connection between plankton and vibrio. Swimmers with broken skin and shellfish eaters are more susceptible to contracting the virus. Both zooplankton and *Vibrio cholera* will also grow tremendously as water temperatures rises (Anas et al. 2021) As a result of global warming, the prevalence of Vibrio-associated infections has obviously increased over the past several decades and had been reached to many nations in Northern Europe (WHO 2021). During the hot summers, such illnesses spread through swimming pools and coastal communities (Leng et al. 2019). Leptospirosis and other water-borne illnesses like gastroenteritis are frequently linked to severe rain and flooding (Alcayna et al. 2022).

Selective fungal adaptation to higher ambient temperatures that mimic those of mammals will occur because of the temperature increase. Due to mammals' body temperatures, pathogenic fungi that are currently not pathogenic to them will therefore be able to infect them in the future (Shokri et al. 2020). Non-infectious diseases can spread due to climatic conditions as well, such as the diseases related to bovines and poultry. For such kind of pathogens, the climate change and global warming are very favorable. The reason might be that due to climate changes including heavy rainfall and high humidity increases the growth of such pathogenic fungi and increase the mycotoxins associated problems in the animals and humans. In addition, there is an increase in food poisonings during the hot summer because of a number of correlated causes, including increased bacterial survivability, an increase in dining out frequency and a higher number of insects and rodents during the hot season (Paterson et al. 2018; El-Sayed and Kamel 2020).

Climatic Changes Effects on Diseases Prevalence

As already described above that Climatic conditions have drastic effects on disease prevalence. Following are described in detail:

1. Insects and Insects Borne Diseases

The spatiotemporal extension of the vector host dimensions, and the onset of the diseases are both influenced by global warming in a complicated but balanced manner (Kholoud et al. 2018). Pathogens that are transmitted by vectors are typically localized to regions where those vectors are found. However, it makes logical sense that the spread of these vector-borne illnesses and the introduction of transmitting vectors to new geographic areas is a main problem. This can be further explained through the spread of diseases to those regions of the world where these parasites were not present earlier (Kading et al. 2018). Due to the spread of their vectors, various diseases, including dengue fever, West Nile fever, chikungunya fever, malaria, leishmaniasis, Lyme disease, and tick-borne encephalitis, have been able to appear in Europe in recent years (Gossner et al. 2018). It is important to not underestimate the potential of new infectious diseases to emerge as a result of the geographic invading of the pathogen harboring vectors. For example, one vector such as the mosquito *Aedes albopictus,* is capable of transmitting at least 22 different arbovirus species, as well as a number of parasitic illnesses (Kading et al. 2018). Several typical instances of newly discovered and remerged diseases that have affected the people and animals or both have been discussed in Table 1.

In North America and Scandinavia, VBDs first appeared because of migration of vectors like ticks. Babesiosis, anaplasmosis, and Powassan encephalitis are among the illnesses transmitted by ticks, while dengue fever and malaria are transmitted by mosquitoes. Other insects, like sandfly spread diseases including leishmaniasis, Boutonneuse fever, and Lyme disease. Similar to this, health records indicate that the southern spread of the eucalyptus in Australia has increased the prevalence of diseases which are co-related to the parasites, bacteria and viruses and considered to be the possible economic losses threats and trade restrictions on animals/animals products in the region (Caminade et al. 2019).

2. Tick Borne Diseases (TBDs)

In Europe and Asia, there are ample evidence linking to the spread of different emerging TBDs (Rubel et al. 2018; Wikel 2018; Michelitsch et al. 2019). Long - term research over

Table 1: Summary of some important (Emerging and Remerging) Human, animal, and zoonotic diseases of bacterial, viral and parasitic origin (Khan et al. 2019)

	Bacterial	Viral	Parasitic
Human	• Bovine Tb • Hemorrhagic colitis (HC) • *Eserchia Coli* (STEC)	• (COVID-19) • (MERS) • SARS • Ebolavirus infection	• Schistosomiasis • Toxoplasmosis • Malaria • Dengue Fever
Animal	• Swine edema • *E. coli*) • *B. henselae* • *Pasteurellosis*	• Swine acute diarrhea syndrome coronavirus (SADS-CoV) • Lumpy Skin Disease	• Fasciolosis • Trypanosomiasis
Zoonoses	• MERSA • Brucellosis • Leptospirosis • Anthrax • Tuberculosis	• West Nile fever • Rabies • Avian influenza • CCHF • Dengue Fever • HIV Infection • Chikungunya virus	• Leishmaniasis • Ascariasis • Babesiosis • Toxoplasmosis • Amebiasis • Giardiasis • Malaria

thirty years of tick development monitoring in Sweden also supported these findings (Rubel et al. 2018). Due to global warming, some tick species in Canada and Europe have moved their habitat to higher altitudes and toward the north, extending their active season and improving their chances of survival in the environment. As a result, tick-borne illnesses like anaplasmosis, Babesiosis, Powassan virus, *Rickettsia helvetica*, *Neoehrlichia mikurensis*, and *Borrelia miyamotoi* disorders have been proliferated (Kayacan and Akgul 2022). Despite the fact that ticks can spread a wider variety of pathogens than any other arthropod vector, luckily, tick-borne diseases typically develop considerably slower than mosquito-borne infections, those have more severe effects on the host and quicker in action TBDs (Wikel 2018). In USA, it has been roughly estimated that about 95% of the emerging diseases have transmitted through the tick bites and these diseases were included in the category of TBDs (Esser et al. 2019). The main tick that is most importantly involved in the spreading of the disease in the Europe, Eurasia, UK and in Germany is *Ixodid racinous*. *Dermacentor reticulatus*, the tick species that transmits the tick-borne encephalitis virus, the Omsk haemorrhagic fever virus, *Rickettsia slovaca*, *Rickettsia raoultii*, *Anaplasma marginale*, *Babesia canis*, *Babesia caballi*, and *Theileria equi*, were also observed to be expanding across Europe and Eurasia (Michelitsch et al. 2019). Similar kind of reports of different parasites emerging from the different area of these regions have also been reported (Jsaenson et al. 2018).

Babesiosis instances in humans have lately been recorded in Canada, Europe, and Japan (Vannier and Krause 2020). Due to global warming, the warmer winters of the past ten years have encouraged tick proliferation (Sergeev et al. 2022). About 11 bacterial tick-borne human diseases, including Rickettsial and Borrelia species, have been identified in Europe in recent years (Pennisi 2021). The infections are propagated epidemiologically by the ticks those are carried by migratory birds. According to literature, at least one tick was present on 16 of the 43 species of migratory birds. Along with *Babesia microti*, *B. capreoli*, and *B. venatorum* to varying degrees, the ticks tested positive for *C. burnetii*, *Rickettsia spp.*, and *R. helvetica* (Lu et al. 2016). In addition to birds, ticks have recently been found to play an epidemiological role in the spread of the zoonotic bacteria *Coxiella burnetii* (Koehler et al. 2019). Additionally, ticks have the ability to spread a wide range of dangerous zoonotic infections (Tokarz et al. 2018; Anas et al. 2021).

Crimean Congo hemorrhagic fever (CCHF) is a second zoonotic tick-borne viral illness that has emerged in Europe and the causative agent of this disease has been transferred from tick and causes many complications in the host body and sometime leads to the death of the host. Due to high mortality in humans, the CCHFV poses a serious threat to public health in Europe. The virus is transmitted to ruminants by the *Hyalomma* tick, and it is currently endemic in Asia, Eastern and Southern Europe, the Middle East, Africa, and the Balkan Peninsula. This tick population have the potential to infiltrate and emerge in new areas due to warmer climatic conditions. Emergence of Piroplasmid (such as *Babesia* and *Theileria*) have also been linked with the tick prevalence in the region. The most significant protozoal disease transmitted by ticks to the cattle is babesiosis and other large ruminants as well as in small ruminants characterized by the onset of high fever and destruction of the red blood cells. As a result of this condition there is hemoglobinuria, which is also the pathognomonic symptom of this particular disease. Babesiosis is a widespread animal health problem that has caused significant financial losses in the veterinary industry. Having zoonotic potential, now it poses risk to the human health also. Human babesiosis is also transferred from the infected animals and its transmission is directly related with the geographic expansion of tick's host induced by the climate changes (Baylis 2017). Babesia have more than 100 identified species and among these *B. microti*, *B. duncani* and *B. divergens have* zoonotic potential (Vannier and Krause 2020). Along with Babesia, other significant infections include *Anaplasma* and *Ehrlichia* (Reaser et al. 2021) those have zoonotic implications. Humans, cattle, horses and dogs all are susceptible to the deadly illness caused by *Anaplasma phagocytophilum* that is transmitted through ticks. Different tick species those are indigenous to Europe (*Ixodes ricinus*), North America (*Ixodes scapularis, Ixodes pacificus* and *Ixodes spinipalpis*), and Asia (*Ixodes persulcatus*) are the possible vectors for the spread of the disease (Vannier and Krause 2020).

Ehrlichia, a similarly related pathogen carried by ticks, can also infect people and animals. *Ehrlichia chaffeensis* and *Ehrlichia ewingii* (Monocytes Ehrlichiosis) can cause the disorders in humans, whereas *Ehrlichia ruminantium* can cause the disease in cattle (Wang et al. 2020). Other Ehrlichia species, such as *Ehrlichia canis*, *Ehrlichia muris*, and *Ehrlichia mineirensis*, can also cause some other types of ehrlichiosis (Ganta 2022).

Due to the spread of ticks, Lyme disease and tick-borne encephalitis (TBE) appeared in Europe. Even in Scandinavia, cases of both diseases have been documented. The prevalence of the disease is rising at alarming level as a result of global warming and the northward spread of the tick vector (Healy et al. 2020). Scandinavian winters have gotten warmer since the middle of the 1980s. Tick borne encephalitis (TBE) has become more prevalent, uniformly, and consistently. Many factors, including climatic change, are thought to be the true cause of this increase (Gilbert 2016; Efstratiou et al. 2021). Lyme borreliosis, incidence in Europe grew over the past ten years, not just in endemic regions but also in new geographic areas, particularly in the Netherlands and Belgium. According to estimates, at least 85,000 persons in Europe contract Lyme borreliosis each year (Hofhuis 2015). In Europe, *Borrelia burgdorferi* and *Borrelia mayonii* are the major pathogens that causes the disease. However, other Borrelia species have been identified as powerful zoonotic spirochetes transmitted by the *Ixodes ricinus* complex in North America and Europe (Nah 2020).

Rabbit fever (tularemia) is another emerging zoonotic disease which is particularly transmitted by the ticks and flies and has been recognized under the umbrella of TBDs (Kukla et al. 2022). Additional ectoparasites like fleas, triatomine bugs, and blood sucking flies including deerfly (*Chrysops spp.*), horsefly (*Tabanus spp.*), and sandfly (*Phlebotomus and Lutzomyia spp.*) were also implicated in the introduction of emerging diseases like tularemia, plague, Leishmaniasis, and trypanosomiasis (El-Sayed and Kamel 2020). Sandfly of the Phlebotomus genus can spread both forms of leishmaniasis. The infections first appeared in European nations, where they afflicted both humans and canines (Bennai et al. 2018). The discovery of sandflies was linked to the growth of leishmaniasis, mostly in dogs and the global warming was documented as a possible factor for their spread around the globe (Kukla et al. 2022).

T. brucei gambiense and *T. brucei rhodesiense*, the protozoa that cause African trypanosomiasis (sleeping sickness), are spread by tsetse flies. It is predicted that 30,000 people would contract the parasite during this century as a result of the vector growth linked to global warming, while 70 million people will be at danger (Moreno et al. 2019). A second type of trypanosomiasis known as Chagas disease, which is induced by *Trypanosoma cruzi* and spread by the bite of the kissing bug, *Triatoma infestans*, or by ingesting water or food contaminated with the feces of the infected bugs, began to appear in Latin America. It was reported that the sickness has spread throughout Central and North America. At the time, the number of Americans who have the illness is estimated to be 300,000 (Montgomery 2016) The plague-causing agent *Yersinia pestis* is transmitted by the flea *Xenopsylla cheopis*. The flea vector and *Yersinia pestis* both benefit from warmer and humid weather (Levy et al. 2021).

3. Rodents and Rodents Borne Diseases

In the epidemiology of disease onset and reemergence, rodents are crucial. They have the capacity to disseminate a variety of zoonotic disease agents, either directly or indirectly (as with plague). Around the globe, the growth and infection graph of rodents is increasing day by day and they are also held responsible for the emergence and re-emergence of many zoonotic diseases (Göotz et al. 2018; Khanal et al. 2022).

Conclusion

As a result of climatic change, the global atmosphere is currently undergoing accelerated destruction, which must be stopped or at least slowed down. In addition to the introduction of infectious diseases, the disruption of healthy ecosystems has long-term, direct and indirect negative repercussions that endanger the lives of people, animals, and plants. In coming years, human and animals are at risk not only in terms of food security but emergence and re-emergence of deadly pathogens outbreaks. Efforts should be made to preserve the natural balance between ecosystems. Humans should play a sensible role to preserve the flora and fauna of the system and avoid making the drastic environmental changes just for their own comfort. Positive contributions should be made to keep the climate safe, and this can only be achieved if all the nations join hands without any discrimination. All the professionals (Doctors, veterinarians, Scientists, and environmental engineers) should join hands and work for the global health.

REFERENCES

Agache I et al., 2022. Climate change and global health: a call to more research and more action. Allergy 77: 1389-1407.

Alcayna T et al., 2022. Climate-sensitive disease outbreaks in the aftermath of extreme climatic events: A scoping review. One Earth 5: 336-350.

Anas A et al., 2021. Dynamics of Vibrio cholerae in a typical tropical lake and estuarine system: potential of remote sensing for risk mapping. Remote Sensing 13: 1034.

Andreassen A et al., 2012. Prevalence of tick-borne encephalitis virus in tick nymphs in relation to climatic factors on the southern coast of Norway. Parasite Vectors 5: 177

Antonenko YN et al., 2013. Penetrating cations enhance uncoupling activity of an- ionic protonophores in mitochondria. PLoS One 8: e61902.

Ariza L et al., 2013. Investigation of a scabies outbreak in a kindergarten in Constance, Germany. European Journal of Clinical Microbiology and Infectious Diseases 32: 373–380

Baker RE et al., 2022. Infectious disease in an era of global change. Nature Reviews Microbiology 20: 193-205.

Baylis M, 2017. Potential impact of climate change on emerging vector- borne and other infections in the UK. Environmental Health 16: 112

Belter M et al., 2020. Coral reef condition: A status report for the Flower Garden Banks.

Bennai K et al., 2018. Molecular detection of Leishmania infantum DNA and host blood meal identification in Phlebotomus in a hypoendemic focus of human leishmaniasis in northern Algeria. PLoS Neglected Tropical Diseases 12: e0006513.

Biagini P et al., 2012. Variola virus in a 300-year-old Siberian mummy. New England Journal of Medicine 367: 2057-2059.

Bojko J et al., 2021. Panopeispora mellora n. gen. n. sp.(microsporidia) infecting Say’s crab (Dyspanopeus sayi) from the Atlantic shoreline of Canada. Journal of Invertebrate Pathology 184: 107652.

Brugueras S et al., 2020. Environmental drivers, climate change and emergent diseases transmitted by mosquitoes and their vectors in southern Europe: A systematic review. Environmental Research 191: 110038.

Buhler KJ et al., 2022. Combining deep sequencing and conventional molecular approaches reveals broad diversity and distribution of fleas and Bartonella in rodents and shrews from Arctic and Subarctic ecosystems. Parasites and Vectors 15: 1-14.

Caminade C et al., 2019. Impact of recent and future climate change on vector-borne diseases. Annals of the New York Academy of Sciences 1436: 157-173.

Cassell JA et al., 2018. Scabies outbreaks in ten care homes for elderly people: a prospective study of clinical features, epidemiology, and treatment outcomes. The Lancet Infectious Diseases 18:894–902

CDC 2017. The Centers for Disease Control and Prevention The burden of schistosomiasis (schisto, bilharzia, snail fever)

Daisy SS, 2019. Hydro-climatic impact on cholera incidence in Dhaka under global warming.

Dhar-Chowdhury P et al., 2017. Dengue seropreva- lence, seroconversion and risk factors in Dhaka, Bangladesh. PLoS Neglected Tropical Diseases 11: e0005475

Dhimal M et al., 2015. Risk factors for the presence of chikungunya and dengue vectors (Aedes aegypti and Aedes albopictus), their altitudinal distribution and climatic determinants of their abundance in central Nepal. PLoS Neglected Tropical Diseases 9: 201-230

Efstratiou A et al., 2021. Tick-Borne Pathogens and Diseases in Greece. Microorganisms 9(8): 1732.

El-Sayed A and Kamel M, 2020. Climatic changes and their role in emergence and re-emergence of diseases. Environmental Science and Pollution Research 27: 22336-22352.

Esser HJ et al., 2019. Risk factors associated with sustained circulation of six zoonotic arboviruses: a systematic review for selection of surveillance sites in non-endemic areas. Parasites and Vectors 121: 1-17.

Ganta RR, 2022. Anaplasmataceae: Ehrlichia and Neorickettsia. Veterinary Microbiology 56: 386-391.

Ghazali D et al., 2018. Climate change impacts on disaster and emergency medicine focusing on mitigation disruptive effects: an international perspective. International Journal of Environmental Research and Public Health 14: 623-633.

Gilbert L, 2016. Louping ill virus in the UK: a review of the hosts, transmission and ecological consequences of control. Experimental and Applied Acarology 68: 363–374.

Goshua A et al., 2021. Addressing climate change and its effects on human health: A call to action for medical schools. Academic Medicine 96: 324-328.

Gossner CM et al., 2018. Increased risk for autochthonous vector-borne infections transmitted by Aedes albopictus in continental Europe. Eurosurveillance 23: 1800268.

Göotz J et al., 2018. Rodent models for Alzheimer disease. Nature Reviews Neuroscience 19: 583-598.

Healy C et al., 2020. Using agent-based models to inform the dynamics of winter tick parasitism of moose. Ecological Complexity 41: 100813.

Hofhuis A, 2015. Continuing increase of tick bites and Lyme disease between 1994 and 2009. Ticks and Tick-Borne Diseases 6: 69–74

Huürlimann E et al., 2011. Toward an open-access global database for mapping, control, and surveillance of neglected tropical diseases. PLoS Neglected Tropical Diseases 5(12): e1404.

Jsaenson TG et al., 2018. The importance of wildlife in the ecology and epidemiology of the TBE virus in Sweden: incidence of human TBE correlates with abundance of deer and hares. Parasites and Vectors 11: 1-18.

Josefsen TD et al., 2018. Bacterial infections and diseases. In: Tryla M, editor. Reindeer and Caribou: Health and disease: CRC Press; pp: 237-272.

Joshi M et al., 2020. Alcoholic Liver Disease Patients Listed for Liver Transplantation: An Overview from 2002-2017. Journal of Gastroenterology and Hepatology Research 9: 3309-3312.

Kading RC et al., 2018. Advanced surveillance and preparedness to meet a new era of invasive vectors and emerging vector-borne diseases. PLoS Neglected Tropical Diseases 12: e0006761.

Kayacan ZC and Akgul O, 2022. Climate change and its extensions in infectious diseases: South-Eastern Europe under focus. South Eastern European Journal of Public Health.

Khan MD et al., 2019. Aggravation of Human Diseases and Climate Change Nexus. International Journal of Environmental Research and Public Health 16(15) 2799.

Khanal S et al., 2022. Potential impact of climate change on the distribution and conservation status of Pterocarpus marsupium, a Near Threatened South Asian medicinal tree species. Ecological Informatics 70: 101722.

Khansins A et al., 2005. Global warming and infectious disease. Archives of Medical Research 36: 689-696.

Kholoud K et al., 2018. Management of leishmaniases in the era of climate change in Morocco. International Journal of Environmental Research and Public Health 15: 1542.

Koehler LM et al., 2019. Comprehensive literature review of the sources of infection and transmission routes of Coxiella burnetii, with particular regard to the criteria of “evidence-based medicine”. Comparative Immunology, Microbiology and Infectious Diseases 64: 67–72.

Kukla R et al., 2022. Francisella tularensis caused cervical lymphadenopathy in little children after a tick bite: Two case reports and a short literature review. Ticks and Tick-borne Diseases 13: 101893.

Kumar P et al., 2022. Prevalence and predictors of water-borne diseases among elderly people in India: evidence from Longitudinal Ageing Study in India, 2017–18. BMC Public Health 22: 1-11.

Leng F et al., 2019. Epidemiology, pathogenetic mechanism, clinical characteristics, and treatment of Vibrio vulnificus infection: a case report and literature review. European Journal of Clinical Microbiology and Infectious Diseases 38: 1999-2004.

Levy DJ et al., 2021. Role of the inhibitor of serine peptidase 2 (ISP2) of Trypanosoma brucei rhodesiense in parasite virulence and modulation of the inflammatory responses of the host. PLoS Neglected Tropical Diseases 15(6): e0009526.

Liu C et al., 2019. Perinatal health of refugee and asylum-seeking women in Sweden 2014–17: a register-based cohort study. European Journal of Public Health s29: 1048-1055.

Lu P et al., 2016. RNA interference and the vaccine effect of a subolesin homolog from the tick Rhipicephalus haemaphysaloides. Experimental and Applied Acarology 68: 113– 126.

Medone P et al., 2015. The impact of climate change on the geographical distribution of two vectors of Chagas disease: implications for the force of infection. Philosophical Transactions of the Royal Society B: Biological Sciences 370: 203-2032.

Michelitsch A et al., 2019. Exploring the reservoir hosts of tick-borne encephalitis virus. Viruses 11: 669.

Montgomery S, 2016. What do we know about Chagas disease in the United States?. The American Journal of Tropical Medicine and Hygiene s95(6): 1225.

Mor S et al., 2018. Climatic influence on anthrax suitability in warming northern latitudes. Scientific Reports 8: 1-9.

Moreno CJG et al., 2019. Trypanosoma brucei interaction with host: Mechanism of VSG release as target for drug discovery for african trypanosomiasis. International Journal of Molecular Sciences 20: 1484.

Morgan ER et al., 2021. Angiostrongylosis in animals and humans in Europe. Pathogens 10: 1236.

Mutlu F and Nacaroglu O, 2019. Examination of Perceptions of Gifted Students about Climate Change and Global Warming. Journal of Baltic Science Education 18: 780-792.

Myhre G et al., 2019. Frequency of extreme precipitation increases extensively with event rareness under global warming. Scientific Reports 9: 1-10.

Nah K, 2020. The potential impact of climate change on the transmission risk of tick-borne encephalitis in Hungary. BMC Infectious Diseases 20: 1-10.

Nava A et al., 2017. The impact of global environmental changes on infectious disease emergence with a focus on risks for Brazil. ILAR Journal 58: 393–400

Ogden NH and Lindsay LR, 2016. Effects of climate and climate change on vectors and vector-borne diseases: ticks are different. Trends in Parasitology 32: 646–656

Pal M et al., 2018. Public health hazards due to unsafe drinking water. Air and Water Borne Diseases 7: 20-34.

Paterson DL et al., 2018. Health risks of flood disasters. Clinical Infectious Diseases 67: 1450-1454.

Pennisi E, 2021. Researchers probe climate as a cause of banner nut years. Science (New York, NY) 374: 1034-1035.

Portier C et al., 2017. A human health perspec- tive on climate change: a report outlining the research needs on the human health effects of climate change. Environmental Health Perspectives/National Institute of Environmental Health.

Reaser JK et al., 2021. Ecological countermeasures for preventing zoonotic disease outbreaks: when ecological restoration is a human health imperative. Restoration Ecology 29: e13357.

Rubel F et al., 2018. Geographical distribution, climate adaptation and vector competence of the Eurasian hard tick Haemaphysalis concinna. Ticks and Tick-borne Diseases 9: 1080-1089.

Sabourin E et al., 2018. Impact of human activities on fasciolosis transmission. Trends in Parasitology 34: 891-903.

Sellers S et al., 2019. Climate change, human health, and social stability: addressing interlinkages. Environmental Health Perspectives 127: 045002.

Sergeev A et al., 2022. The role of climate change in the spread of vectors and vector-borne disease in Windsor-Essex County. Environmental Health Review 65: 95-101.

Shokri A et al., 2020. Impacts of flood on health of Iranian population: Infectious diseases with an emphasis on parasitic infections. Parasite Epidemiology and Control 9: e00144.

Tokarz R et al., 2018. Identification of novel viruses in Amblyomma americanum, Dermacentor variabilis, and Ixodes scapularis ticks. mSphere 3: e00614–e00617.

Vannier E and Krause PJ, 2020. Babesiosis. In: Hunter's tropical medicine and emerging infectious diseases: Ryan ET, Hill DR, Solomon T, Naomi E, Trimothy P, editors. Elsevier; pp: 799–802.

Wang Y et al., 2020. Multiple Ehrlichia chaffeensis genes critical for its persistent infection in a vertebrate host are identified by random mutagenesis coupled with in vivo infection assessment. Infection and Immunity 88: e00316-20.

Weilnhammer V et al., 2019. Extreme Weather Events in Europe and Their Possible Health Consequences; a Systematic Review. Environmental Epidemiology 3: 432-433.

WHO, 2017. WHO report 2017: Global environmental change.

Wikel SK, 2018. Ticks and tick-borne infections: complex ecology, agents, and host interactions. Veterinary Sciences 5: 60-87.

World Health Organization, 2021. Advances in science and risk assessment tools for Vibrio parahaemolyticus and V. vulnificus associated with seafood: Meeting report (Vol. 35). Food and Agriculture Organization.

Wu XX et al., 2014. Impact of global change on transmission of human infectious diseases. Science China Earth Sciences 57: 189–203.

Zhang S et al., 2019. Zoonotic source attribution of Salmonella enterica serotype Typhimurium using genomic surveillance data, United States. Emerging Infectious Diseases 25: 82-102.

Zhang Y et al., 2017. Co-benefits of global, domestic, and sectoral greenhouse gas mitigation for US air quality and human health in 2050. Environmental Research Letters 12: 114033

31

Conservation Medicine and Biodiversity in Iraq

AUTHORS DETAIL

Rana M Al-Obaidi [1*], Ridha Hasan Hussein[2], Ahmed Sami Shaker [3], Questan Ali Ameen[4], Korsh Ararat [5], Zaid Kh. Khidhir [6], Sehand K Arif [7] and Israa Hameed Abd Al-Sada[8]

[1]Department of Basic Sciences, College of Veterinary Medicine, University of Sulaimani, Sulaymaniyah, KRG, Iraq.
[3]Department of Animal Production, Directorate of Agricultural Research. Sulaymaniyah, KRG, Iraq
[4,6]Department of Animal science, College of Agricultural Engineering, University of Sulaimani, Sulaymaniyah, KRG, Iraq
[2,5,7]Department of Biology, College of Science, University of Sulaimani, Sulaymaniyah, KRG, Iraq.
[8]Department of Anatomy & Histology, College of Veterinary Medicine, University of Sulaimani, Sulaymaniyah, KRG, Iraq.
*Corresponding author: rana.ubaidi@univsul.edu.iq

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INTRODUCTION

A major breakthrough in both medicine and environmentalism, is conservation medicine which was not put in use until the mid-1990s. It may be difficult to see the connection between human health, wildlife health, and ecosystem health in practice, but this is a fundamental concept for conservation medicine. Risk posed by animal diseases that can be transmitted to humans are of paramount importance. The threat of transmitted diseases standing in the central correlation between zoonotic diseases (animal to human), and zoo-anthroponoses (human to animal) for example covid-19 virus is zoonotic, zoo-anthroponotic, and it is also an emerging infectious diseases transmitted between human and between animals (Dawood 2022). Regarding human impact on environment and wild animals, burning vast swaths of forest to make way for farmland will displace a wild animal species that will then infect a domesticated animal. As the infected domestic animal makes its way into the human food chain, it introduces a new health risk to humans. These relationships are rarely considered in traditional approaches to environmental, animal and human health. For the field of conservation medicine, connections like these are crucial. Many different disciplines of experts must collaborate on this concern (Fowler and Miller 2007).

Conservation Medicine

Human, animal and ecosystem health are all interconnected, so it makes sense to take a multidisciplinary approach for conservation in order to protect all forms of life, including humanity (Fowler and Miller 2007; Deem 2016). It is the practice of using medicine to protect both human and animal populations (Fig. 1). Documenting, assessing, monitoring, modifying, and/or preventing diseases in wildlife may all fall within the scope of conservation medicine (Keatts 2021). A "new" initiative called One Health followed this comprehensive conservation medicine strategy for global healthcare (Prescott and Logan 2019).

One Health

One Health is a strategy that acknowledges the nearby connection between human health, animal health, and our shared environment. One Health is not a new concept, but its significance has grown in recent years. This is because numerous factors have altered human, animal, plant, and environmental interactions (CDC 2022).

Eco Health

Health sciences are usually focus on health, or health care and their relations to multiple academic disciplines, including Science, technology, engineering, and mathematics disciplines in addition to emerging patient safety disciplines such as prevention, reduction, reporting and analysis of unnecessary harm. In comparison, the Eco Health concept can be described as an ecosystem approach to health, with an emphasis on environmental and socioeconomic issues, and was conceived by disease ecologists engaged in biodiversity conservation (Roger et al. 2016).

Threats to Biodiversity

The current rate of species extinction is thought to be between one thousand and one hundred thousand times faster than the average rate over the last several billion years. Most of the major challenges facing biodiversity today can be traced back to rising human populations, consumption, and mobility (Bellard et al. 2022).

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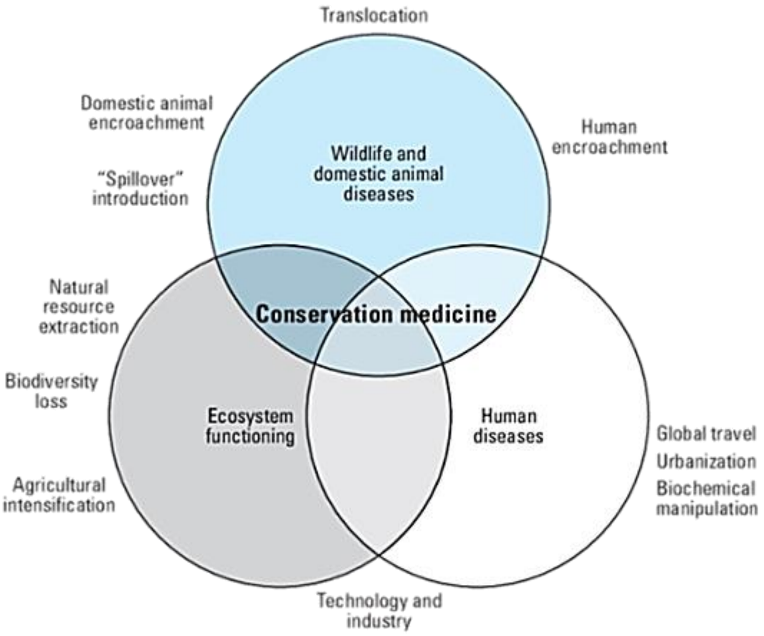
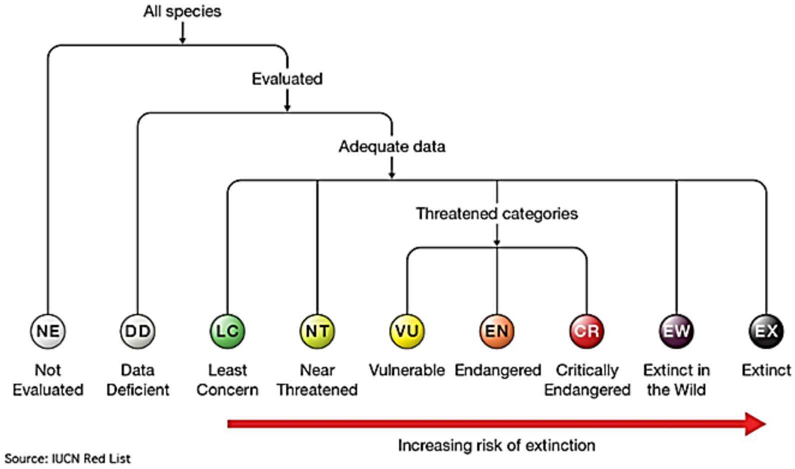


Fig. 1: The main elements converging under the Consortium for Conservation Medicine. Conservation medicine combines conservation biology, wildlife veterinary medicine and public health (Aguirre et al. 2002).



Source: IUCN Red List

Fig. 2: The International Union for Conservation of Nature (IUCN) unveiled this assessment system in 1994. It contains explicit criteria and categories to classify the conservation status of individual species on the basis of their probability of extinction (IUCN 2009).

Biodiversity refers to the wide range of organisms and environments that emerge on our planet. Genetic variability, species diversity, and ecosystem diversity all contribute to the "biodiversity" (Wall et al. 1999). In general, the tropics have a higher biodiversity than other parts of the world because of the favorable environment and high crop growth found there. Fewer than 10% of Earth's surface is occupied by tropical forest ecosystems, yet these are native to approximately 90% of the planet's species (Gallery 2014).

Numerous species were officially designated as "rare, endangered, or threatened" in 1996. Furthermore, scientists predict that millions of additional species are in threat but are not officially recognized. There are currently 16,119 of the 40,177 species evaluated by the IUCN Red List that are recognized as being in danger of extinction (Fig. 2) (IUCN 2011). Habitat loss, invasive species, over exploitation (excessive hunting and fishing stress), pollution, and global warming are the five main drivers of species extinction (IUCN 2009).

Numerous distinct types of direct threats to conservation were determined by The International Union for Conservation of Nature which include Construction of residences and businesses; Agriculture; Energy generation and mineral extraction; Highway construction and service; the usage of biological resources; human interferences and actions that modify, destroy, or simply interfere habitats and species from exhibiting natural behaviors; changes to natural systems; invasive and harmful species, pathogens, and genes; Extreme weather conditions and Climate change and Pollution (Salafsky et al. 2008).

Conservation Medicine in Iraq

Although conservation medicine is still a relatively unknown field in Iraq, however, it is becoming increasingly important in today's human-modified landscapes due to the rise in habitat loss, degradation, and human-wildlife conflicts (UNDP 2010).

It's crucial to adapt the expansion of this sector to Iraq, considering the issues like the manner local residents consider nature and interact with animals. Conservation areas in Iraq are in a prime position to study the results of ecological shifts and human interference with native species (UNDP 2014).

After the 2003 invasion of Iraq by allied forces, many organizational and political changes were made, including the establishment of Iraq's first Ministry of Environment (MOEI). Slowly but surely, this new Ministry began to take over environmental legislation from the Ministry of Health's environmental department (UNDP 2015).

Iraq took the first steps forward into correcting its biodiversity loss problem in 2009, when it joined the Convention on Biological Diversity (UN Environment 2017). As required by the all Parties to the Convention, Iraq submitted its first national report to the CBD Secretariat, to safeguard Iraq's unique flora, fauna, and ecosystems which formulated after the submission of the 4th national report of Iraq on the current state of biodiversity in the country (UNDP 2010).

Recognizing the need for Iraq to improve its environmental preservation system, Dr. Azzam Alwash (a founding member of the board of trustees of American University of Iraq, Sulaimani) worked on the restoration of the marshes and founded “Nature Iraq”, an Iraqi NGO focused on the preservation of Iraq’s environment and cultural heritage. Dr. Alwash is working now on issues of water and the environment through Nature Iraq and American University of Iraq, Sulaimani to promote the idea of cooperation on water management and making water an instrument of peace rather than the source of tension in the future Middle East (AUIS 2016).

Numerous major and minor ecoregions of the Palearctic Realm frame Iraq's terrestrial ecosystems (UNDP 2018) (Fig. 3). The five most important ecoregions of Iraq have been described below; These are Iraq's five most important ecoregions.

Tigris-Euphrates alluvial salt marsh (PA0906) – 35600 km2 Area

It is characterized by a vast inland delta formed by the Euphrates, Tigris, and Karun Rivers, despite being surrounded by deserts and dry shrubland. The weather is hot and dry, with subtropical characteristics (Frenken 2009).

Biodiversity

Many endemic and semi-endemic species, as well as those that migrate from Eurasia and the Gulf to breed in the winter, rely on this ecoregion for survival. Depending on the list of Important Bird Areas (IBAs) of Iraq authored by (Evans (1994) and complemented by a list of significant wetlands in Iraq by (Key Biodiversity Area) KBA Project (Nature Iraq 2011), the first locations chosen for field investigations were concentrated in this area (Scott 1995).

The Salt Marsh ecoregion is home to a number of threatened bird species due to its status as an Endemic Bird Area (Table 1) (Al-obeidi et al. 2011).

Based on findings from the KBA survey conducted in southern Iraq between 2005 and 2008, it is recognized that of the 159 bird species registered, 34 are of conservation concern, with eight of those being globally threatened (Salim 2009). The status of the rare mammal species that have been documented in this ecoregion is poorly understood, but there is indication that unique species went back (Garstecki and Amr 2011). Most of the wetland’s areas in southern Iraq, down to the Fao peninsula, are now inhabited by two species that had previously been wiped out by the 2003 re-flooding. Mammals, insects, amphibians, and reptiles are also frequently reported but have not been adequately studied despite their prevalence (Bedair et al. 2006).

Conservation Status

Due to ecosystem transformation brought on by the drainage of the marshlands in large parts of southern Iraq, this terrestrial zone is classified as "Critical/Endangered."(UNDP 2010).

Arabian Desert and East Sahero-Arabian Xeric Shrublands (PA1303) – 1851300 km2 Area

The Arabian Peninsula's desert ecosystem, which extends from Oman to Iraq, is habitat to an extremely limited variety of plant and animal life. It's a dry area, with only 125 millimeters of rain annually, but there are still pockets of oasis here and there (Dearborn and Kark 2010). In some places, a brackish salt flats exists, and some of those in Iraq have actually been kept into service as reservoirs for water (e.g., Razaza Lake). The Bedouins (nomads) start moving their flocks of goats, sheep, and camels from one part of the region to another depending on the time of year (Frenken 2009).

Biodiversity

Previous research and the KBA Project's preliminary results have shed light on the region's biodiversity, but the area remains one of the least studied aspects in the country (Al-obeidi et al. 2011). Wolves, hyena, gazelle, wild boar, fox, bat and other notable mammal species were once thought to be

Table 1: Salt Marsh ecoregion species in southern Iraq

Local name	Scientific name	Reference
Asian Imperial Eagle	*Aquila heliacal*	(Salim 2009)
Asian water buffalo	*Bubalus bubalis*	(Bedair et al. 2006)
Basra Reed Warbler	*Acrocephalus griseldis*	(Salim 2009)
Basra reed-warbler	*Acrocephalus griseldis*	(Al-obeidi et al. 2011)
Black-tailed Godwit	*Limosa limosa*	(Salim 2009)
Bunn'sShort-tailed Bandicoot Rat	*Erythronesokia bunnii*	(Garstecki and Amr 2011)
Ferruginous Duck	*Aythya nyroca*	(Salim 2009)
Golden Jackal	*Canis aureus*	(Bedair et al. 2006)
Greater Spotted Eagle	*Aquila clanga*	(Salim 2009)
Honey badger	*Mellivora capensis*	(Bedair et al. 2006)
Iraq babbler	*Turdoides altirostris*	(Al-obeidi et al. 2011)
Macqueen's Bustard	*Chlamydotis macqueenii*	(Salim 2009)
Marbled Duck	*Marmaronetta angustirostris*	(Salim 2009)
Mesopotamian gerbil	*Gerbillus mesopotamiae*	(Garstecki and Amr 2011)
Red Fox	*Vulpes vulpes*	(Bedair et al. 2006)
Rüppell's Fox	*Vulpes rueppelli*	(Bedair et al. 2006)
Small Asian Mongoose	*Herpestes auropunctatus*	(Bedair et al. 2006)
smooth-coated otter	*Lutra perspicillata maxwelli*	(Garstecki and Amr 2011)
White-headed Duck	*Oxyura leucocephala*	(Salim 2009)
wild boar	*Sus scrofa*	(Bedair et al. 2006)
wolves	*Canis lupis*	(Bedair et al. 2006)

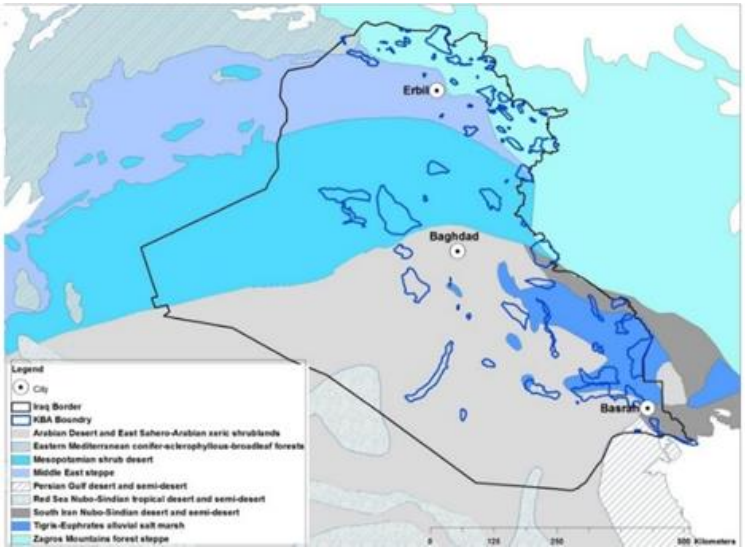

Erbil
Baghdad
Basrah
Legend
City
Iraq Border
KBA Boundry
Arabian Desert and East Sahero-Arabian xeric shrublands
Eastern Mediterranean conifer-sclerophyllous-broadleaf forests
Mesopotamian shrub desert
Middle East steppe
Persian Gulf desert and semi-desert
Red Sea Nubo-Sindian tropical desert and semi-desert
South Iran Nubo-Sindian desert and semi-desert
Tigris-Euphrates alluvial salt marsh
Zagros Mountains forest steppe
0
125
250
500 Kilometers

Fig. 3: Terrestrial and Aquatic Eco-regions of Iraq and Key Biodiversity Areas (KBAs): WWF and Nature Iraq (UNDP 2018).

Table 2: Salt Marsh ecoregion species in southern Iraq (Al-obeidi et al., 2011; Ehab Eid et al. 2020)

Local name	Scientific name
Arabian Oryx	*Oryx leucoryx*
Asian Houbara	*Chlamydotis macqueenii*
Asiatic Cheetah	*Acinonyx jubatus*
Bar-tailed Lark	*Ammomanes cincture*
Cream-colored Courser	*Cursorius cursor*
Desert Finch	*Rhodospiza obsoletus*
Desert Wheatear	*Oenanthe deserti*
Eurasian Eagle Owl	*Bubo bubo*
Macqueen's Bustard (Spotted Sandgrouse)	*Pterocles senegallus*
Steppe Eagle	*Aquila nipalensis*
Temminck's Lark	*Eremophila bilopha*

present in this area, but their current distribution and abundance are unknown. Table 2 lists several species that have almost certainly disappeared from the region (Ehab Eid et al. 2020).

Conservation Status

This terrestrial zone is classified as "Critical/Endangered." The KBA Project's surveys provide some background on the area, but security issues have prevented more in-depth research (UNDP 2010).

Mesopotamian Shrub Desert (PA1320)–211000 km2 Area

In this area temperatures are dry and hot, much like the Arabian Desert. It comprises of Parts of the Syrian Desert and the plain region to the north, which spans the Fertile Crescent between the valleys of the Tigris and Euphrates rivers (UNDP 2018).

Biodiversity

Augla, Gasr Muhaiwir, Attariya plains, and Abu Habba are some of the few terrestrial areas mentioned by Evans (1994) as being significant for birds. Numerous species and other significant migratory species between Eurasia and Asia rely on the region's stable and seasonal wetlands as well as its occasionally wet drainage/wadis (Heshmati and Squires 2013). There could be significant wolves, hyena, gazelle, wild boar, and other animal populations in the area. Four key species that used to be present in this ecoregion are now gone for good. Multiple examples of these species had already been hunted to extinction by the middle of the twentieth century. Table 3 shows the mammals found in the Mesopotamian Shrub Desert ecoregion, which is similar to what is shown for the Arabian Desert and East Arabian Xeric Shrublands (PA1303) ecoregion. Along with the Mehely's horseshoe bat (*Rhinolophus mehelyi*) and the desert hedgehog (*Paraechinus aethiopicus*), the Longeared Hedgehog (*Hemiechinus auritus*) and the Euphrates jerboa (similar to a gerbil) are also common in this ecoregion. Little is known about the current status of any of these poorly studied species in this area (Al-Sheikhly et al. 2015).

Conservation Status

The earth's surface in this area is particularly vulnerable. The KBA Project 2009–2010 surveys provide some data for this area, but security concerns have prevented extensive research there (UNDP 2015).

Middle East Steppe (PA0812) – 132300 km2 Area

This region extended from western Jordan and south-western Syria to northern Iraq, overlapping the Tigris-Euphrates River Valleys and ending in the foothills of the Zagros Mountains near Iran. The region is divided into a dry and moist steppe made up mainly open shrub/grasslands. Continental climate is characterized by hot, dry summers, low annual rainfall (less than 250 mm) and cold, frosty winters (Al-Ansari et al., 2018).

Biodiversity

Several species of conservation concern breed in this ecoregion's varied from dry to wet ecosystems (IBP 2008). Species with southern origins, documented in an IUCN report migrate toward north for the winter (IUCN 2011).
The typical habitats of the large mammals of the ecoregions listed in Table 4. These habitats include marshes and semiarid grasslands. Again, not much is known about the status of these and other types of mammals, amphibians, and reptiles (Keith et al. 2020).

Conservation Status

This area is particularly vulnerable. The WWF (2006) claims that centuries of grazing and wood cutting have diminished this area to its present form, which was once a steppe-forest. The KBA Project surveys conducted within Kurdistan provide some data for this area, but the border region with Syria has seen less intensive research due to security concerns (UN Environment 2017).

Zagros Mountains Forest Steppe (PA0446) – 397800 km2 Area

This ecoregion stretches from the northwest to the southeast of Iran, and its northernmost border with Iraq's mountainous Kurdish regions (known as Iraqi Kurdistan). Over a wide area, there is a mountain-forest-steppe ecoregion with a semi-arid temperate climate and annual precipitation of 400–800 millimeters that falls primarily in the winter and spring. Temperatures in the winter can fall to 25 degrees Celsius or more, while summer highs can reach 40 degrees Celsius or higher (Anderson et al. in WWF 2006).

Biodiversity

In addition to the varied steppe native plants, the region is home to oak-dominated deciduous forests and pistachio-almond groves (Xu et al., 2020). The Eastern Mediterranean conifer-sclerophyllous broadleaf forest (PA1207) ecoregion probably includes a small portion of Iraq, including the Dohuk governorate, where a remnant pine forest of Pinus brutia can be found (in Zawita, northwest of Dohuk city). The forest on the southern side of the range is more steppic, with fewer trees and more shrubs (UNDP 2010; UN Environment 2017).
Only three geostationary sites were identified by Evans (1994) as being significant to birds in this ecoregion. In particular, these are found in the region separating Iraq and Turkey (Benavi, Dure and Ser Amadia). Table 5 summarize Birds of this ecoregion (Ararat et al. 2011). The mammals of the Zagros Mountains Forest Steppe ecoregion include the brown bear, wolves, jackals, wild cats, leopard, gazelle, roe deer, and wild goat. It has recently been confirmed that the critically endangered Persian fallow deer (*Dama mesopotamica*) is present in the western foothills of the mountainous region, but their existence in Iraq is still unknown at this point. Anatolia's Zagros Mountains and their neighboring ranges are home to five lizard species found nowhere else on Earth (Anderson in WWF 2006). Because of the numerous mine fields along the boundary between Iran and Iraq, studying leopards there is extremely challenging (Schwartzstein 2014).

Conservation Status

This ecoregion is located in a "Critical/Endangered" terrestrial zone, but due to regulations legislated by the

Table 3: Mesopotamian Shrub Desert ecoregion species in southern Iraq.

Local name	Scientific name	Reference
Arabian Oryx	*Oryx leucoryx*	(Al-Sheikhly et al. 2015)
Arabian Ostrich	*Struthio camelus syriacus*	(Al-Sheikhly et al. 2015)
Asiatic Cheetah	*Acinonyx jubatus*	(Al-Sheikhly et al. 2015)
Caracals	*Caracal caracal*	(UNDP 2010)
Goitered gazelles	*Gazella subgutturosa*	(UNDP 2010)
Golden jackals	*Canis aureus*	(UNDP 2010)
Jungle cats	*Felis chaus*	(UNDP 2010)
Leopards	*Panthera pardus*	(Al-Sheikhly et al. 2015)
Macqueen's Bustard	*Chlamydotis macqueenii*	(Al-Sheikhly et al. 2015)
Mesopotamian gerbil	*Gerbillus mesopotamiae*	(UNDP 2010)
Rüppell's Fox	*Vulpes rueppelli*	(UNDP 2010)
Sociable Lapwing	*Vanellus gregarious*	(Al-Sheikhly et al. 2015)
Striped hyenas	*Hyaena hyaena*	(UNDP 2010)
wild boars	*Sus scrofa*	(UNDP 2010)
wolves	*Canis lupus*	(UNDP 2010)

Table 4: Mesopotamian Shrub Desert ecoregion species in southern Iraq.

Local name	Scientific name	Reference
Armenian Gull	*Larus armenicus*	(Salim et al. 2020)
Caracals	*Caracal caracal*	(Keith et al. 2020)
Common otter	*Lutra lutra*	(Keith et al. 2020)
Eastern Imperial Eagle	*Aquila heliacal*	(Salim et al. 2020)
Egyptian Vulture	*Neophron percnopterus*	(IBP 2008)
Eurasian griffon vulture	*Gyps fulvus*	(IBP 2008)
Eurasian Teal	*Anas crecca*	(Salim et al. 2020)
European badgers	*Meles meles*	(Keith et al. 2020)
Finsch's Wheatear	*Oenanthe finschii*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
Goitered gazelle	*Gazella subgutturosa*	(Keith et al. 2020)
Golden jackals	*Canis aureus*	(Keith et al. 2020)
Graceful Prinia	*Prinia gracilis*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
Greater flamingos	*Phoenicopterus ruber*	(IUCN 2011)
Greater Horseshoe Bat	*Rhinolophus ferrumequinum*	(Keith et al. 2020)
Greater White-fronted Goose	*Anser albifrons*	(Salim et al. 2020)
Iraq Babbler	*Turdoides altirostris*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
jungle cats	*Felis chaus*	(Keith et al. 2020)
Lesser kestrel	*Falco naumanni*	(IBP 2008)
Lesser White-fronted Goose	*Anser erythropus*	(Salim et al. 2020)
Long-legged Buzzard	*Buteo rufinus*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
Mongoose species	*Herpestes sp.*	(Keith et al. 2020)
Northern Lapwing	*Vanellus vanellus*	(Salim et al. 2020)
Pin-tailed sandgrouse	*Pterocles alchata*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
pygmy cormorant	*Phalacrocorax pygmeus*	(IUCN 2011)
Red fox	*Vulpesvulpes*	(Keith et al. 2020)
Red-wattled Lapwing	*Vanellus indicus*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
See-see Partridge	*Ammoperdix griseogularis*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
Slender-billed Gull	*Chroicocephalus genei*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
Steppe Buzzard	*Buteo buteo vulpinus*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
Turtle dove	*Streptopelia turtur*	(Ararat et al. 2011; Al-Kerwi et al. 2022)
wild boar	*Sus scrofa*	(Keith et al. 2020)
wildcats	*Felis silvestris*	(Keith et al. 2020)
wolves	*Canis lupus*	(Keith et al. 2020)

Kurdistan Regional Government, it receives more rights than other similar regions (e.g., seasonal fishing moratoriums, hunting and wood cutting controls). Extensive land mines cover large swaths of the border regions with Iran and Turkey, primarily at high altitude sites (UNDP 2018).

Conservation of Iraq Mammals

Mammal research in Iraq has not been performed by scientists in over 30 years because it demands specialized knowledge, techniques, and tools that are not readily available in the country. Because of the lack of data on the

Table 5: Zagros Mountains Forest Steppe (PA0446) (Ararat et al. 2011)

Local name	Scientific name
Chukar Partridge	*Alectoris chukar*
Egyptian Vulture	*Neophron percnopterus*
Eurasian Crag Martin	*Ptyonoprogne rupestris*
Eurasian Griffon Vulture	*Gyps fulvus*
Golden Eagle	*Aquila chrysaetos*
Greater Spotted Eagle	*Aquila clanga*
Kurdistan Wheatear	*Oenanthe xanthoprymna*
Lesser Kestrel	*Falco naumanni*
Long-legged Buzzard	*Buteo rufinus*
Smyrna Bunting	*Emberiza semenowi*
Syrian Woodpecker	*Dendrocopos syriacus*

status of these species in Iraq, Nature Iraq recommends intense caution. Many species are going extinct in Iraq and the surrounding area because hunting and ecosystems damages are not being restricted at this time (Nature Iraq 2007; Ahmed and Majeed 2020). As it's known, no native Iraqi species is unnecessary to sustain life. Several of these processes are crucial to human well-being. The co - evolution of Iraq's ecosystems over thousands of years means that the loss of even one of these species could have devastating long-term effects (UNDP 2018).

Native Felines

The local felines of Iraq, such as the Jungle cat, Wildcat, Caracal, and Sand cat, are sociable and human-friendly. It is now understood that human violence and hybridization with feral cats create serious dangers to the Wildcat. The loss of its wetland habitat, uncontrollable hunting, and the poisoning of other animals by farmers are all major threats to the survival of the rare and elusive jungle cat in Iraq. Poisoning and excessive hunting are also threats to the Caracal. As far as Nature Iraq is concerned, all of the country's native felines need to be given the highest level of protection (Ahmed and Majeed 2020; ANIMALIA 2022).

Native Canines

The striped hyena, golden jackal, sand fox, red fox, fennec fox, and Arabian wolf are just a few examples of non-aggressive native canines that serve important ecological roles. They play a crucial role in cleaning carcasses off the desert floor and are the primary controllers of rodents in the wild. Iraq's native canines are in serious risk because of widespread persecution by herders and the cultural stigma that surrounds some of these species (Al-Sheikhly et al. 2020). It's possible that the striped hyena, a species that is considered to be near-threatened, should be listed as endangered in Iraq (Al-Sheikhly et al. 2015).

As a result, smaller and larger canines tend to disappear, while Red foxes and Golden jackals flourish. The outcomes are neither preferable nor useful, and may have lasting negative effects on the ecosystem (Aguirre et al. 2002).

Other Native Mammal Species

Although they aren't harmful to humans, small mammals like the Cape hare, Indian crested porcupine, Honey badger, and Desert hedgehog replace essential and interesting ecological roles (Nature Iraq 2007).

Feral Species

Numerous parts of Iraq, especially those close to cities, have a serious issue with feral animals. Wild animals are less likely to approach humans, but they may be a rabies carrier, while feral animals are more likely to carry rabies, kill native species, and cause extensive damage to ecosystems. As a matter of both human and environmental safety, Nature Iraq endorses the eradication of feral animals (Nature Iraq 2007).

Nuisance Animals

Certain native animals can become annoying if they regularly engage in harmful or dangerous behaviors toward humans. An animal that is discovered in a workplace or residence may be considered a nuisance if it has a history of scavenging trash or causing other damage, is visibly ill, or displays aggressive behaviour without violence. Nature Iraq agrees that nuisance animals should be managed, but that individuals, not animals, are often the source of the problem. Nature Iraq is against the use of poison, traps, or any other inhumane means to get rid of nuisance animals. The most effective scientific procedures should be used for pest animal management (Nature Iraq 2007; Doherty et al. 2021).

Birds

Birds can be considered as one of the main components of the field of conservation medicine and it can be used as indicator for its connection with the environment and human health. According to Birdlife International (2022) in Iraq there are 74 important bird areas (IBAs) (BirdLife International 2022) and approximately 410 bird species (Salim et al. 2012). More than half of these species are in Iraq and migratory birds located within three main flyways (routes the birds follow as they migrate between nesting and wintering areas) including Black Sea/Mediterranean, East Asia/East Africa, and Central Asia flyways (Fig. 4) (BirdLife Data Zone 2010). Birds can transmit different zoonotic diseases that can cause problems for human beings, wild birds and domesticated birds, such as avian influenza, tuberculosis, velogenic Newcastle disease, histoplasmosis, escherichiosis, salmonellosis, cryptococcosis, campylobacterosis, cryptosporidiosis, and erysipelas (Boseret et al. 2013).

Bird flu (H5, N1) and its different strains in addition to some highly pathogenic avian influenza (HPAI) which, besides birds can be transmitted to mammals such as cats, dogs, swine and humans. Since the last two decades migratory birds,

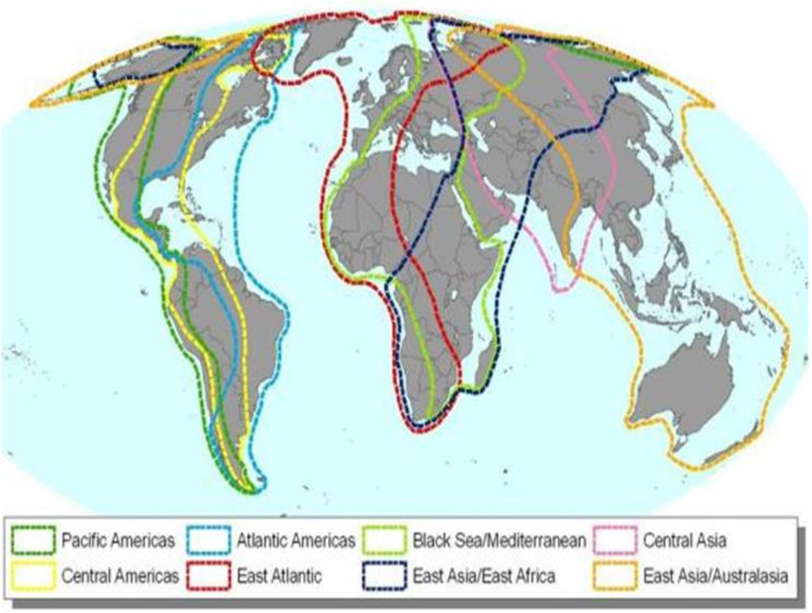


Fig. 4: Migratory flyways for wild birds, Birdlife Data Zone (2010).

are a reservoir of the avian flu which have a global impact to the public health and economic issues and may cause death of millions of both wild and domesticated birds in Iraq and around the world. Furthermore, there are 19 bird species in Iraq which is considered as globally threatened species (Birdlife International 2022). In general, vultures' numbers are declining around the world because they are very sensitive to the changes in the ecosystems. In Iraq there are four vulture species including; Bearded Vulture (*Gypaetus barbatus*), Eurasian Griffon Vulture (*Gyps fulvus*), Cinereous Vulture (*Aegypius monachus*) and the Egyptian Vulture (*Neophron percnopterus*) based on the International Union for Conservation of Nature (IUCN). Red List species are endangered (EN), which are summer breeder and passage migrant to mountains of Kurdistan region in Iraq (Salim 2009; Raheem et al. 2021; Salim et al. 2012; Abdulrahman 2022).

There are different factors that cause the decrease of the vultures populations such as; intentional poisoning, collusion with powerlines and hunting; but based on different studies in India one of the main reason of disappearing the vultures is due to diclofenac use, which is an anti-inflammatory drug used for treating arthritis in domesticated animals when they die and the vultures feed on them the diclofenac traces as a secondary metabolite causes kidney failure in the vultures particularly in the Gyps spp. (Meteyer et al. 2005). Diclofenac is banned by several countries to prevent the extinction of vultures, unfortunately it is still used by veterinarians in Iraq. However, there isn't any recorded cases for vultures death due to diclofenac in Iraq, but, vultures feed mostly on the left wild boar carcasses because most of the hunters leave them when they hunt wild boars (Alabdaly 2021).

Marine Ecosystems

The inland fishing industry of Iraq is vital to the country's economy, and it relies on the Tigris-Euphrates River system scheme, its lakes, and seasonal floods (with a flooded area of 15,000 to 20,000 km2). Iraq's principal aquifers are the Tigris and Euphrates rivers as well as their tributaries. Natural lakes (39%), reservoirs and dams (13.3%), rivers and their branches (3.7%), and marshlands (44%), make up the overland fresh water sources that cover between 600,000 and 700,000 ha. Managing, stocking, and enhancing widespread cultural procedures have the potential to develop these resources. Fishing in many smaller lakes and rivers and reservoirs can be improved through stocking and management strategies that account for the unique characteristics of each fishery. If done correctly, stocking and other processes, such as quasi-culture techniques, have the potential to greatly increase fishing. Carps of the genus Cyprinus are the backbone of the inland fisheries, while barbs of the genus Barbus are the most economically significant of Iraq's native fishes (Unlu 2012).

Iraq's major polluting factor is the disposal of contaminated wastewater into water systems along the river's journey. This includes sewage, industrial water, and residues from hospitals, slaughterhouses, washing and lubrication garages etc., and it also includes pollution from brackish water returning from agricultural lands and industrial wastes, all together form 75% of polluted natural water (Lateef et al. 2020). The chemical system of the river is altered by human activity due to the regular overflow of industrial and health wastes (Mohsin et al. 2021).

Since the turn of the century, freshwater effluents from the Tigris and Euphrates rivers have decreased, and salt contamination from the Arabian Gulf has had a negative effect on Shatt al-Arab water quality (Moyel and Hussain 2015; Al-Asadi et al. 2022). Several native cyprinid species, including *Luciobarbus xanthopetrus*, *Arabibarbus grypus*, *Luciobarbus kersin*, *Mesopotamichthys sharpeyi*, and *Carasobarbus luteus*, have either vanished from or seen a significant decline in vast quantities in certain Iraqi rivers (Mhaisen et al. 2015; Mohamed et al. 2017; Al-Thahaibawi et al. 2019).

According to recent research conducted in Iraq, while native species are the core of a fish groupings and an important part of diversity, the presence of exotic species is a sign of biological pollution and a significant deviation from natural conditions, particularly when the proportion of exotic species in an assemblage is high or when it is introduced on purpose. As a result of environmental deterioration, the most tolerant species at last go to extinct (Mohamed and Al-Jubouri 2020).

Zoonotic Transmission of Diseases and Human Health

Farmers and others who work with or are exposed to sick farm animals may themselves become ill. People who regularly come into contact with equines, such as horses and donkeys, are more likely to contract glanders. Close contact with cattle can lead to cutaneous anthrax infection rather than the inhalation type that is more common in places like slaughterhouses, tanneries, and wool mills (Lassen et al. 2014). Pregnant women and people with compromised immune systems are at a higher risk of getting Q fever, toxoplasmosis, and listeria if they come into close contact with newborn sheep (and enzootic abortion in those who are pregnant). Infected sheep can spread the echinococcosis-causing tapeworm to humans via contaminated food and water, which strikes immuno-compromised individuals primarily (Lassen et al. 2014). Hepatitis E is highly dependent on contact to animal products, with pork being a major source of infection in Western countries (Ji et al. 2021).

Iraq is unique in the Middle East due to its agricultural industry and abundance of natural resources (CDC 2020). The country is home to a wide variety of animals, including sheep, goats, cattle, water buffaloes, horses, donkeys, mules, and camels. New and expanding conservation issues and emerging diseases put stress on the long-term survival of threatened wild animals in the wild and in captivity, and have negative effects on ecosystems and public health as a result of human activity (Martin 2019).

UNEP predicts that by the year 2020, industrial farming of pigs and chickens in particular will be a major risk factor for the spread of zoonotic diseases. Anthropogenic environmental destruction and rising global meat consumption are major contributors to the rise of zoonotic pandemics (Espinosa et al. 2020; Glidden et al. 2021).

Effects of Intentional Eradication Efforts

Due to a lack of knowledge about the kinetics of species, many elimination efforts have failed and are now considered wasteful and counterproductive. It is possible that non-target species, such as the threatened species Egyptian Vulture, have died from starvation as a result of these programs' negative impacts, i.e., the application of poisons to eliminate (Skartsi et al. 2014).

Attempts to eradicate wild species as a result of the latest H5N1/bird flu and H1N1/swine flu pandemics are counterproductive. No wild boar species have been linked to the spread of the present swine flu strain (Sun et al. 2020). For instance, if the H1NI virus was already present in boar populations, culling them could make matters worse by encouraging the spread of the virus and leading to an increase in human contact with pigs. An ecologist "Aldo Leopold" writes that "To keep every cog and wheel is the first precaution of intelligent tinkering,", and this is the golden rule for wildlife conservation in Iraq. In the absence of sufficient actual studies, Nature Iraq endorses this cautious approach. The clinical adage "First, do no harm" should serve as the core philosophy for wildlife management in Iraq until further notice (Green and Grosholz 2021).

Conclusion

Iraq is unique in the Middle East due to its agricultural industry and abundance of natural resources and is home to a wide variety of animals. Although conservation medicine is still a relatively unknown field in Iraq, it is becoming increasingly important in today's human-modified landscapes due to the rise in habitat loss, degradation, and human-wildlife conflicts. Regarding human impact on environment and wild animals, any destructive action in environment will displace a wild animal species that will then infect a domesticated animal which in turn finds its way into the human food chain and introduces a new health risk to humans. These relationships are rarely considered in traditional approaches to environmental, animal, and human health. For the field of conservation medicine, connections like these are crucial. Many different disciplines of experts must collaborate on this concern.

Recommendations

It's crucial to adapt the expansion of this sector to Iraq by considering issues like the way local residents consider nature and interact with animals. Conservation areas in Iraq are in a prime position to study the results of ecological shifts and human interference with native species.

REFERENCES

Abdulrahman B, 2022. Egyptian Vulture Conservation Project In Iraq—Nature Iraq. Nature Iraq.

Al-Ansari N et al., 2018. Water quality within the Tigris and Euphrates catchments. Journal of Earth Sciences and Geotechnical Engineering 8(3): 95-121.

Aguirre AA et al., 2002. Conservation Medicine: Ecological Health in Practice, Oxford University Press, UK.

Ahmed SH and Majeed SI, 2020. Monitoring of the Wild Mammal Fauna in Bamo Mountain in Northern Iraq (Kurdistan) for the First Time Using Camera Trap Method and Raising Awareness for Its Conservation. Bulletin of the Iraq Natural History Museum P-ISSN: 1017-8678, E-ISSN: 2311-9799.

Alabdaly YZ, 2021. Effect of diclofenac on the pharmacokinetics of ciprofloxacin in quail. Iraqi Journal of Veterinary Sciences 35(4): 777–781.

Al-Asadi SAR et al., 2022. Seawater intrusion into Shatt Al-Arab River, Northwest Arabian/Persian Gulf. Journal of Applied Water Engineering and Research 10: 1080.

Al-Kerwi M et al., 2022. A Review of The Current Status of Migratory Wild Birds in Iraq and Syria. Al-Qadisiyah Journal for Agriculture Sciences 12: 131–142.

Al-obeidi L et al., 2011. Key Biodiversity Survey of Iraq 2010 Site Review.

Al-Sheikhly O et al., 2020. Distribution update. The grey wolf in Iraq: Notes on its current distribution, major threats and conservation status 22(1): 1–7.

Al-Sheikhly O et al., 2015. Checklist of the Mammals of Iraq (Chordata: Mammalia). Bonn Zoological Bulletin 64: 33–58.

Al-Thahaibawi BMH et al., 2019. Fish Assemblage Structure in Al-Huwaizah marsh southern of Iraq after inscribed on the World Heritage List. Iraqi Journal of Science 2019: 1430–1441.

Anderson EP et al., 2006. Transforming tropical rivers: An environmental perspective on hydropower development in Costa Rica. Aquatic Conservation: Marine and Freshwater Ecosystems 16(7): 679–693.

ANIMALIA, 2022. Cats of Iraq. Animalia https://animalia.bio/lists/country/cats-of-iraq?page=1

Ararat KO et al., 2011. Breeding birds in Iraq: important new discoveries. Sandgrouse 33(1): 12-33.

AUIS, 2016. Azzam Alwash. The American University of Iraq Sulaimani. https://auis.edu.krd/?q=board/azzam-alwash

Bedair HM et al., 2006. Iraq's southern marshes something special to be conserved; A Case Study. Marsh Bulletin 2(1): 99-126.

Bellard C et al., 2022. Ranking threats to biodiversity and why it doesn't matter. Nature Communications 13(1): Article # 1.

BirdLife Data Zone, 2010. http://datazone.birdlife.org/sowb/casestudy/the-flyways-concept-can-help-coordinate-global-efforts-to-conserve-migratory-birds

BirdLife International, 2022. BirdLife International. https://www.birdlife.org/

Boseret G et al., 2013. Zoonoses in pet birds: Review and perspectives. Veterinary Research 44(1): 36.

CDC, 2020. Types of Anthrax | CDC. https://www.cdc.gov/anthrax/basics/types/index.html

CDC, 2022. One Health Basics. https://www.cdc.gov/onehealth/basics/index.html

Dawood KA, 2022. A review on Covid-19 (Corona Virus Disease), Transmission and Pathological effects. Kufa Journal for Veterinary Medical Sciences 13(1): Article # 1.

Dearborn DC and Kark S, 2010. Motivations for conserving urban biodiversity. Conservation Biology: The Journal of the Society for Conservation Biology 24(2): 432–440.

Deem SL, 2016. Conservation Medicine: A Solution-Based Approach for Saving Nonhuman Primates. Ethnoprimatology 2016: 63–76.

Doherty TS et al., 2021. Human disturbance causes widespread disruption of animal movement. Nature Ecology and Evolution 5(4): Article # 4.

Ehab Eid et al., 2020. National Red data book of mammals in Jordan. IUCN Regional Office for West Asia, Amman, Jordan.

Espinosa R et al., 2020. Infectious Diseases and Meat Production. Environmental and Resource Economics 76(4): 1019–1044.

Evans MI, 1994. Application of Strategic Fuzzy Assessment for Environmental Planning; Case of Bird Watch Zoning in Wetlands. BirdLife International.

Fowler ME and Miller ER, 2007. Zoo and Wild Animal Medicine Current Therapy, Elsevier Health Sciences.

Frenken K, 2009. Irrigation in the Middle East region in figures—AQUASTAT Survey 2008.

Gallery RE, 2014. Ecology of Tropical Rain Forests. In: RK Monson editor. Ecology and the Environment: Springer; pp: 247–272.

Garstecki T and Amr Z, 2011. Biodiversity and Ecosystem Management in the Iraqi Marshlands. Screening Study on Potential World Heritage Nomination. IUCN ROWA, Jordan pp: 189.

Glidden CK et al., 2021. Human-mediated impacts on biodiversity and the consequences for zoonotic disease spillover. Current Biology 31(19): 1342–1361.

Green SJ and Grosholz ED, 2021. Functional eradication as a framework for invasive species control. Frontiers in Ecology and the Environment 19(2): 98–107.

Heshmati GA and Squires VR, 2013. Combating Desertification in Asia, Africa and the Middle East, Springer.

IBP, 2008. Iraq Ecology, Nature Protection Laws and Regulations, Handbook Volume 1 Strategic Information and Regulations.

IUCN, 2009. Extinction crisis continues apace. IUCN. https://www.iucn.org/content/extinction-crisis-continues-apace

IUCN, 2011. IUCN Red List of Threatened Species, Criteria and Facts, Britannica. https://www.britannica.com/topic/IUCN-Red-List-of-Threatened-Species

Ji Y et al., 2021. Estimating the burden and modeling mitigation strategies of pork-related hepatitis E virus foodborne transmission in representative European countries. One Health 13: 100350.

Keatts LO, 2021. Implications of Zoonoses from Hunting and Use of Wildlife in North American Arctic and Boreal Biomes: Pandemic Potential, Monitoring, and Mitigation. Frontiers in Public Health 9: 627-654.

Keith DA, 2020. IUCN Global Ecosystem Typology 2.0 Descriptive profiles for biomes and ecosystem functional groups.

Lassen B et al., 2014. Cryptosporidiosis – an occupational risk and a disregarded disease in Estonia. Acta Veterinaria Scandinavica 56(1): 36.

Lateef ZQ et al., 2020. Evaluation of Water Quality Parameters in Shatt AL-Arab, Southern Iraq, Using Spatial Analysis. Hydrology 7(4): Article # 4.

Martin, 2019. UN Report: Nature's Dangerous Decline "Unprecedented"; Species Extinction Rates "Accelerating." United Nations Sustainable Development. https://www.un.org/sustainabledevelopment/blog/2019/05/nature-decline-unprecedented report/#:~:text=The%20Report%20finds%20that%20around,20%25%2C%20mostly%20since%201900.

Meteyer CU et al., 2005. Pathology and Proposed Pathophysiology of Diclofenac Poisoning in Free-Living and Experimentally Exposed Oriental White-Backed Vultures (Gyps Bengalensis). Journal of Wildlife Diseases 41(4): 707–716.

Mhaisen FT et al., 2015. Nematodes and Acanthocephalans of Fishes from the Euphrates River at Al-Musaib City, Mid Iraq. American Journal of Biology and Life Science 4(3): 108- 115.

Mohamed AR and Al- Jubouri M, 2020. A comparison study on growth, reproductive and food habit of Mesopotamichthys sharpeyi in the Al-Diwaniya River, middle of Iraq. International Journal of Fisheries and Aquatic Studies 8(2): 49-56

Mohamed AR et al., 2017. Status of Fish Assemblage Structure in the Garmat Ali River, Iraq. Journal of Agriculture and Veterinary Science 10: 17–22.

Mohsin RM, 2021. Effective quality control of a municipal wastewater treatment plant using Geographic information systems: A Review. Journal of Engineering 27(7): 66–72.

Moyel M and Hussain N, 2015. Water quality assessment of the Shatt al-Arab River, Southern Iraq. Journal of Coastal Life Medicine 3(6): 259-64.

Nature Iraq, 2007. Conservation of Iraq Mammals (NI-0409-001).

Nature Iraq, 2011. Key Biodiversity Areas project report. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/http://www.natureiraq.org/uploads/5/2/9/9/52997379/animal_and_bird_trade_and_hunting_in_iraq_-_ni-0711-01_4.pdf

Prescott SL and Logan AC, 2019. Planetary Health: From the Wellspring of Holistic Medicine to Personal and Public Health Imperative. Explore 15(2): 98–106.

Raheem SS et al., 2021. A review of the shorebirds of Iraq: Status and habitats. Marsh Bulletin 16(2): 144-164.

Roger F et al., 2016. One Health and Eco Health: The same wine in different bottles? Infection Ecology and Epidemiology 6: 30978.

Salafsky N et al., 2008. A Standard Lexicon for Biodiversity Conservation: Unified Classifications of Threats and Actions. Conservation Biology 22(4): 897–911.

Salim MA et al., 2020. Diversity of Avian Fauna of Al-Dalmaj Wetlands and the surrounding terrestrial areas, Iraq. Journal of Physics: Conference Series 1664(1): 012105.

Salim MA et al., 2012. An annotated checklist of the birds of Iraq. Sandgrouse 34(1): 3–44.

Salim M, 2009. A summary of birds recorded in the marshes of southern Iraq, 2005-2008. BioRisk 3: 205–219.

Schwartzstein P, 2014. "For Leopards in Iran and Iraq, Land Mines Are a Surprising Refuge", National Geography/Animals, 21 Dec 2014. https://www.nationalgeographic.com/animals/article/141219-persian-leopard-iran-iraq-land-mine

Scott D, 1995. A directory of wetlands in the Middle East. Iraq. IUCN, Gland and IWRB, Slimbridge.

Skartsi T et al., 2014. Assessment of the illegal use of poison in Natura 2000 sites for the Egyptian Vulture in Greece and Bulgaria during the period 2003-2012. Technical report, WWF, Greece, Athens.

Sun H et al., 2020. Prevalent Eurasian avian-like H1N1 swine influenza virus with 2009 pandemic viral genes facilitating human infection. Proceedings of the National Academy of Sciences 117(29): 17204–17210.

UN Environment, 2017. Annual Report of Iraq-Convention on Biological Diversity. UNEP-UN Environment Programme.

UNDP, 2010. CBD Fourth National Report.

UNDP, 2014. 5th National Report to the Convention on Biological Diversity.

UNDP, 2018. 6th National Report of Iraq to The Convention on Biological Diversity.

UNDP, 2015. Iraq’s National Biodiversity Strategy and Action Plan (2015-2020). Ministry of Environment, Republic of Iraq.

Unlu E, 2012. Fisheries and Aquaculture in the Euphrates and Tigris Basin in Turkey. In: FAO. 2014. Report of the Expert Meeting on the Review of Fisheries and Aquaculture Activities in the Tigris Euphrates Basin, Erbil, Iraq, 11–12 Nov 2012.

Wall DH et al, 1999. National Research Council (US) Committee on Noneconomic and Economic Value. What is Biodiversity? In Perspectives on Biodiversity: Valuing Its Role in an Everchanging World. National Academies Press, US.

Xu X et al., 2020. Mapping Asia plants: Current status on floristic information in Southwest Asia. Global Ecologyand Conservation 33: e01962

32

A Mutually Beneficial and Dynamic Relationship between Human and Animals

AUTHORS DETAIL

Hawzhin Jamal Mahmood [1*], Hadia Karim Zorab [2], Sazan Qadir Amin[3], Hana Hassan Mustafa [4]

[1]Department of Anatomy and Histopathology, College of Veterinary Medicine, University of Sulaimani, Sulaimani, Kurdistan Region-Iraq.
[2]Department of Anatomy and Histopathology, College of Veterinary Medicine, University of Sulaimani, Sulaimani, Kurdistan Region-Iraq.
[3]Department of Anatomy and Histopathology, College of Veterinary Medicine, University of Sulaimani, Sulaimani, Kurdistan Region-Iraq.
[4]Department of Surgery and Theriogenology, College of Veterinary Medicine, University of Sulaimani, Sulaimani, Kurdistan Region-Iraq.
*Corresponding author: Hawzhin Jamal Mahmood

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INTRODUCTION

HAR is represented as a mutually beneficial and dynamic relationship between human and animals. It usually influences wellbeing and health or both. HAR is similar to the appreciated association bond found between parents and their offspring called the parent-infant bond (Zinn and Beck 2014). HAR returns back to the thousands of years, while studies in the field are rather new. Some researchers have begun to study the effects of human relations with other animals, and they found that interacting with animals can increase our activity and mental health (Matchock 2015), in addition, enhance aspects of our daily lives (Carpenter et al. 2022). On the other hand, some researches focuses on HAR may have positive results for animals' health, anxiety, and fear too (Gourkow et al. 2014). The relationship between a companion animal and a human have positive effect on physical, psychological, and social health by lowering the levels of depression and anxiety symptoms (Bolstad et al. 2021), and reduce loneliness. This fact was discovered clearly during the COVID-19 pandemic, and it is determined that there is a significant association between the pet ownership, loneliness, and social support (Kretzler et al. 2022). Along with the social support effect of HAR, pets play a variety of major responsibilities in modern health care by decreasing cortisol, increasing oxytocin, lowering blood pressure, reducing heart attack, and reducing obesity (Bauman et al. 2011; McCune et al. 2014; Chandler et al. 2017; Applebaum et al. 2021). The companion animals have an important role in the education of children at school, as well as they have the potential role to improve children socio-emotional and mental development. Therefore the effects of HAR is used in educational contexts, like training programs for social competence, reading skills or by introducing animals mostly dog into the classroom (Hediger and Beetz 2015).

Bonds Between Human and Animal

There are Four Types of Bonds Discovered Between Human and Animal (Fig. 1) which are as follows:

1. Animal assisted therapy: this is the relationship between human and animals for treatment of some chronic disease until human sense get better. Therapy animal supports numerous people and facilitated by a trainer who is not a member in the intervention (Jones et al. 2019).
2. Animal assisted activity: In this particular type of bond, a companion animal enhances ownership quality of life (Winkle et al. 2020).
3. Animal assisted education: it is companion animal act as structured activity meant to improve a participant's academic or educational abilities (Melson and Fine 2015). For example the teacher introduce dog to their classroom to promote language of the children in the preschool stage (BEETZ 2012).
4. Service assistance animal: this type of animal assist the disable person who cannot do daily activity well (Parenti et al. 2013). Service animal contrast from therapy animal; they are support only one person (Lerner 2019).

History of Human and Animal Relationship

The history of HAR goes back into more than 50,000 years ago (Braje 2011), when the humans started to domesticate the animals for many reasons like, source of food (meat and milk), work, transportation and pest control. In the past, hunting was unproductive, but then humans began transitioning their life from gathering food by hunting of wild animals to a farming and domasticated animals, and they knew it was the right way to have food on their hand (Svizzero 2016). Ancient cave drawing and domestication of animals show how animals have a significant role in human civilization for thousands of years. Hence animals have been respected as essential partners in human survival,

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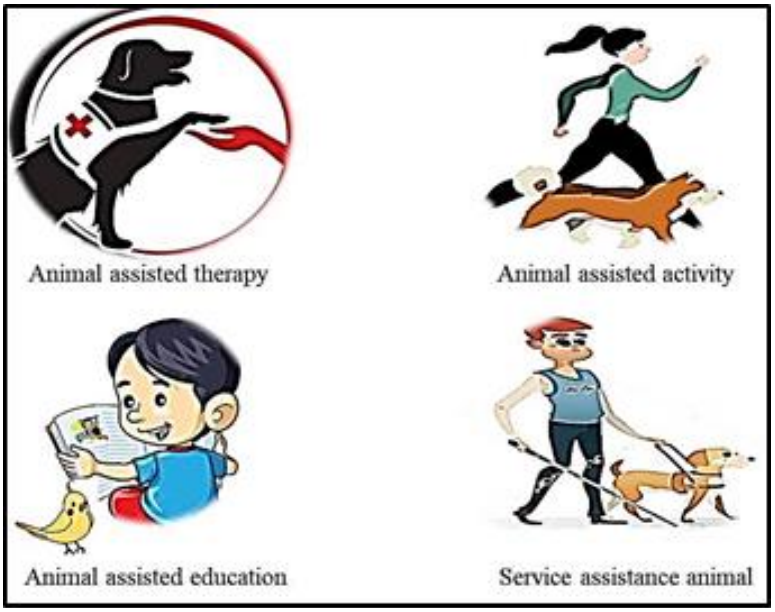

Fig. 1: Type of bond between human and animal relationship.

health and healing (Wei-Haas 2018). Over 14,000 years ago in archaeological evidence exposes domestic wolves; they lived with humans and dogs, and they were respected as directors, and their performance as equal partners in hunting and fishing (Serpell 2010). Besides, 9000 years ago, dogs and cats have important roles in developing agriculture, because dogs were supported in herding and farming, although cat excluded rodent that cause disease to harvested grains (Ikram 2015). In the early Greek and Roman empires, dog was very associative, and they were reserved as hunters, herders, and guardians. On the other hand, they were loyal and beloved pets to their owner (Coren 2002).

Benefit of Human and Animal Relationship on Social Support

According to recent studies, illustrate there are emotional relationship present between human and animals, and some people believe that companion animal is one of the family members because it provide comfort, safety, and social support , and reducing loneliness, anxiety, and depression on its owner (Meehan et al. 2017; Hui Gan et al. 2020).

Reduce Loneliness

Loneliness is a contributor to the isolation of social interactions and relationships with family, friends, neighbors, and society at large. So loneliness is associated with health-risk behaviors; including loss of appetite, immunosuppression, and removal of daily physical activity (Segerstrom 2008; Algren et al. 2020). Some researchers investigated that there is a significant relationship between owning of animal and reducing loneliness. This condition is truly observed in aged people; as they did not marry or they were divorced or they became widowed, and they have heigh levels of attachment towards animals (Krause-Parello 2012). The main cause of ambivalence is over emotional expression that is suffer from loneliness. This sign is exactly reduced by the support of companion animal, and it can produce a barrier to the negative effects of loneliness (Bryan et al. 2014). At the beginning of the COVID-19 pandemic, many researchers investigated the virus effectiveness on human health which leads to the mortality, while during a time of lockdowns, several researchers did research on the problems that produced by the corona virus, and one of the effect of the virus is social isolation, the effect of which can be reduced by relationship and interaction with companion animal (Brodeur et al. 2021, Kretzler et al. 2022), as a result, owning animal could be supported during the COVID-19 pandemic because of interactions with companion animals encouraging physical communication, and have physiological and psychological benefits (Hunjan and Reddy 2020).

Reduce Depression

Depression is mean imbalance in emotional, psychological and physiological behaviour of a person. It is effect on how human feel, think, and handle daily activities. HAR provided to be helpful to heartbroken adults who is alone, and do not have any human social support. HAR also reduces their depression by playing with dog or cat, watching fish in water pool, or birds flying in sky (Arora and Gupta 2017). Companion animal can remove our attention from worries, sadness, and daily problem to glad and joyful day. HAR increases the feeling of security, happiness and self-worth and reduces the feelings of loneliness. Companion animals also support us in changing our behaviour and provide us unconditional love which lead to the reduction of depression (Mueller et al. 2018). For instance, compare people who have animal and older adults and who reported being more attached to their companion animals, have lower levels of depression and psychological distresses as well as greater quality of life (Teo and Thomas 2019).

Reduce Anxiety

Anxiety is a feeling of nervousness such as worry and fear that arises from environmental and genetic causes including the experience of childhood adversity; exposure to traumatic events such as immigration; serious illness and death of a relative (Dowsett et al. 2020). Companion animals have a powerful effect on reducing anxiety and have important role in increasing of social emotion, and their ability to respond their owner in times of distress (Brooks et al. 2018). HAR reduce anxiety and has proven to brighten up both a pet's and a pet owner's life, through play and interaction between them and reducing cortisol hormone which is the stress hormone in the body in contrast to increase in oxytocin which is anti- stress hormone is increased in the body (Petersson et al. 2017). According to the study on the influence of HAR on mental and physical health during the corona virus lockdown in the United Kingdom; companion animals were perceived as being able to reduce anxiety, and their owner described positive experiences of how their animals had influenced their current life situation and how their animals had provided a constant source of friendship and emotional support (Shoesmith et al. 2021).

HAR Encourages Physical Activity and Promotes Health

Most of studies of human and animal interaction suggested owning a companion animal because it has beneficial effects on human wellbeing and activity, and owning animal such as a dog, cat, bird, fish, or horse is related with less appointments to the doctor (Headey and Grabka 2007; Thodberg 2014). HAR is improving health through regular physical activity between companion animal and owner (Brooks et al. 2018). Physical activity is preventing the cause of a wide range of diseases along with a reduction in the risk of early death (Warburton and Bredin 2017). Dog ownership has been associated with regular physical activity which causes weight management ;leading to the reduce incidence, severity, and clinical symptoms of osteoarthritis (Duncan et al. 2020). HAR also has positive effect on prevention of obesity because of the regular daily exercise with pet (Chandler et al. 2017). Riding a horse is used to treat patient with neurological disorder because during horse riding, rider's pelvis is moves easy and rhythmic, in addition to the regulation of breathing rhythm and strength of the muscle. The rider on the horse's back reaches to the optimal physical health (Lönker et al. 2020). Companion animals have a major role in aging health issue because they have influence on physical activity and sedentary behaviour in community-dwelling older adults. According to the investigation aged people walked with their pet on an average of 20 min longer in a day than aged people who do not have pet (Dall et al. 2017). Today, a large percentage of the population in the world are at the high-risk of cardiovascular disease and hypertension. This condition is produce by a variety of abnormal health behaviour. Some researches were investigated that HAR is associated with the beneficial effect of lowering blood pressure and reduce heart disease. Blood pressures were significantly lower when stroking and talking to dog than chatting and reading (BEETZ 2012). HAR has important therapeutic role in cardiovascular health (McCune et al. 2014). For this reason, the American Heart Association issued a scientific statement represented in one research that relationship with companion animal especially dog decreases the hazard of cardiovascular disease (Levine et al. 2013). Another therapeutic effect of HAR is on the neuroendocrine pathways involving oxytocin which plays a direct role in mammalian emotions and social behaviour. In the brain, these neuropeptides act as neurotransmitters and neuromodulators, with important actions in the autonomic nervous system. Although previous research has focused largely on main functions of oxytocin having an important role in reducing stress and fear, because Hypothalamic–pituitary–adrenal axis activity can be significantly attenuated by oxytocin (Applebaum et al. 2021). Oxytocin's level increase during HAR and companion animals create barriers on stress response both prior and after activation of the stress response system (Tedeschi et al. 2015, Robino 2019). In contrast, HAR cause decrease cortisol which is the stress hormone that cause depression and anxiety in human (Beetz et al. 2012). It increases the speaking and activity among people (Tedeschi et al. 2015) such as dogs helped increasing the level of communication among persons with Alzheimer's disease (McCabe et al. 2002; Cevizci et al. 2013). Owning a pet has been an important role in developed health care. A research was conducted to determine the role of dogs with the ability to predict and prevent their owner when seizures will occur (Brown and Goldstein 2011), Another study observed the character of dog to identify sings of dropping in blood sugar for people with diabetes (Wells et al. 2008). Finally, service animals help people with a wide variety of illnesses and disabilities (Walczak et al. 2012).

Healthy Child Development with HAR

Now-a-days children grow up in households with companion animal, and they view the animal as a personal friend or a member of their family and it doesn't matter either it is cat, dog, bird, fish, reptile, guinea pig, or any other pets (Melson and Fine 2015). Along with providing social support and removing stress, companion animal has a major role on children immune system by reduction on the level of cortisol (Bennett 2011). HAR may have beneficial role on learning and language development, especially in developing preschool children because it increased the speed on motor tasks and their intelligence of them (Gee et al. 2007). The presence of a well-trained dog in the classroom of preschool children is more helpful for teacher (Gee et al. 2010), and improve students attention to the subject. Additionally, teachers favour taking their dogs or other pets to school and integrating them into their lessons (BEETZ 2012). Down syndrome's children learning and behaviour also encourages through HAR. According to a study, children suffering from Down syndrome and owning a dog were more responsive to teacher, parent, and sibling and showed more attention in the presence of a live dog as compare to a toy dog (Hediger and Turner 2014). Another important role of HAR is promotion of child responsibility and self-confidence. When you do not have enough time for pet care, your children is felt responsibility by filling up a pet's bowl with water or sprinkling food into a fish tank, feeding a pet at the right times, not disturbing them while they sleep, and never take away a pet's favourite toy (Purewal et al. 2017). HAR can assist children to understand how to be kind, caring, and respectful (Hediger and Turner 2014). Finally, children who are growing up with pets have better health and are more active because pets are active and play with children most of the time (Hui Gan et al. 2020).

The Effect of HAR on Animal Health and Production

According to a study, HAR had an impact on animal's health and behaviour (Napolitano et al. 2020). There is a degree of relation present between animal and human being that advanced and express through their mutual behaviour (Ellingsen et al. 2014). According to the investigation, some species of animals have the positive relationship with human and it is represented by absence of fear reactions, and animals are easier to handle. Positive interactions like gentle slaps and talking with animals display positive effect and reduce fear in animals. Providing food is a successful strategy for attracting animals, and stockpersons with positive outlooks (Rushen and De Passille 2015). Several behaviour tests determined that farm animals are more attractive toward stationary owner with squatting position comparing to the owner actively moving toward them, and in standing position. They and recognize the individual person who treat them well than those who act in an aggressive mode (Waiblinger et al. 2006). In contrast the negative effect on farm animals likes shouting and hitting, causes poor animal welfare, leading to the stress, and fear responses towards humans (Mota-Rojas et al. 2020). It is important to remind that HAR have direct and indirect effects on the animal and poultry health, behaviour, and product quality like milk, meat, and egg production (Fig. 2) (Napolitano et al. 2020). HAR effect the well-being of pet animals too. According to a research, HAR reduced the level of cortisol in saliva of dog and increased the release of oxytocin, when dog share house and environment with owner, and they are healthier, active and joyful than dog in shelter, because dog with owner has direct contact, play, walking and stroking. Positive HAR make the pet animals confident, relaxed, better sleeping quality and lower heart rate. Eventually companion animals are healthier and associative than the animals without owner (Rault et al. 2020).

The Role of HAR During Disaster

Clearly, HAR is a strong bond between animals and human and is helpful for human during disaster like burned by bushfires or drowned by floods(Thompson 2013). HAR is beneficial for our daily life, so it is important to protect and save pet animals during disaster. Fortunately, some pet owners feel very close to their pets to the extent that many animal owners would put their own lives at risk to save their animal in times of emergency and disaster. In fact, people who own and care for farm or pet animals, wish to save lives of their companion animals, hence it has positive benefits on the personalities, society, and humankind (Smith 2012). When person is preventing the life of animal from risk, it is no different from saving human and child life, and it is a high point of personality actions (Thompson 2013). During the natural disasters, the owner should be advice how to prevent their animals, and give them disaster response planning. It is a growing program which focus the need for rigorous preparation in order to minimize the impact of disasters (Taylor et al. 2015). As a final point, we should remind that more than half of the world's households contain at least one pet animal. So, it is important to keep animal life before and after natural disasters, because we do not forget that how animal can provide benefits for the physical and mental health and well-being of humans beyond the disaster event (Thompson 2018).

Is HAR Always Beneficial?

Although HAR have a beneficial effect on health, emotion and social support but all HAR is not positive. Some species of animals are not better for close relationships with humans, and some human interaction with animal is unfriendly, or they may be allergic to animals or terrified of them (Dhont et al. 2019). Additionally, companion animals may act as a source of zoonotic infection transmission to their owners (Overgaauw et al. 2020) because of their close communication with owner like sleeping in beds and owner's face licking (Stull et al. 2013). Human may be infected with pet-associated zoonosis through bites, scratches, direct contact with skin and mucous membranes

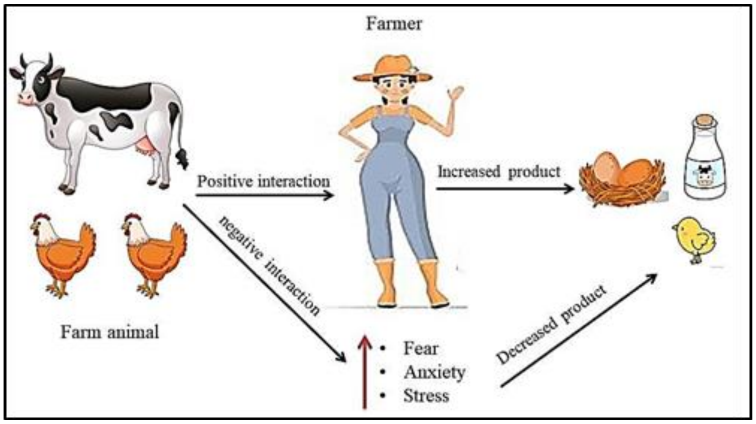

Fig. 1: HAR impact on product quality.

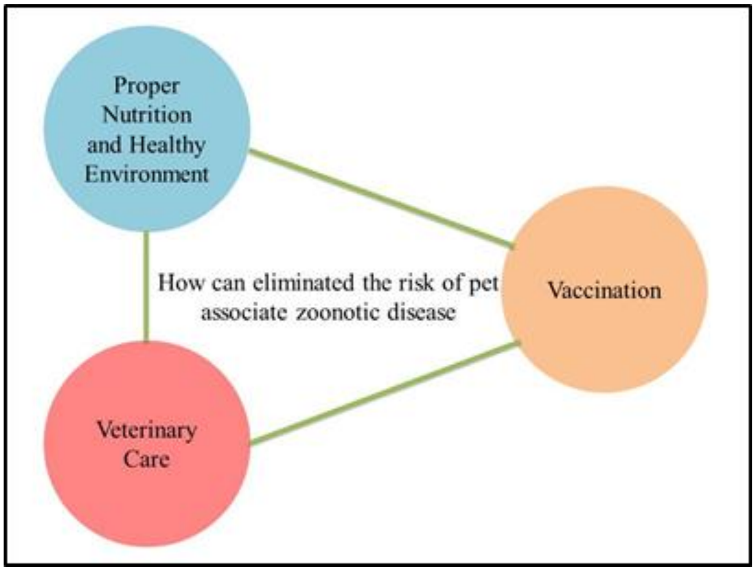
Proper Nutrition and Healthy Environment
How can eliminated the risk of pet associate zoonotic disease
Vaccination
Veterinary Care

Fig. 3: Three beneficial approaches to prevent companion animal's health, and reduce the risk and transmission of zoonotic diseases

of the animal, or contact with animal saliva, urine and other body fluids or secretions, inhalation of infectious aerosols or droplets and through the bite of arthropods and other invertebrate vectors (Mani and Maguire 2009; O'Neil 2018). People with increased risk for zoonotic disease transmission include pregnant women, teenager (age < 5 year) and aged people (age ≥ 65 year) and immunocompromised patient like patient return back from cancer that obtained a new pet and the physicians do not question about pet contact, and not discuss the risks of zoonotic diseases with the patient's immune status (Stull et al. 2013; Stull et al. 2015).

Now, the veterinarian has a major role in decreasing the risk of zoonotic disease transition by information on pet husbandry and preventive health measures. Health care provide information about pet associated diseases and safe pet ownership, especially to people who do not own a pet before. Likewise physician has a role to advice a patient relation with animals during meeting, principally with patients at high risk (Stull et al. 2015; van Herten and Meijboom 2019). Companion animals and people often share the same environment; the presence of concurrent sick pets may also cause owner to get ill. Therefore, pets receive mutual benefit from their associations with people when provided with comfortable homes, good nutrition, and veterinary care. During adoption of pets, there are a number of factors that must be pointed, including selecting an appropriate pet for the family, its lifestyle, training, nutrition, exercise, and veterinary care as needed (McCune et al. 2014). Zoonotic diseases have worldwide distribution, causing important economic losses and effecting the human health, animal health. Therefore the vaccination of animals and humans to prevent inter-species zoonotic disease transmission is an essential intervention (Carpenter et al. 2022). Fig. 3 shows three beneficial approaches to prevent companion animal's health and reduce the risk and transmission of zoonotic diseases.

Conclusion

It is evident that significant progress has been achieved in our knowledge and understanding of the mutual benefit of HAR for the well-being of humans and animals because HAR reduces the effect of social isolation disorder and improve emotional wellbeing. It has an important role in decreasing the risk factor of some chronic diseases like obesity and cardiovascular disease. Sometimes companion animal is a close friend of children, and is a source of unconditional love and comfort. Beneficial HAR reduces fear and anxiety in animals and promotes animal health and production. Finally, animal health protection is crucial in preventing human health and declining the risk and transmission of zoonotic diseases.

REFERENCES

Algren MH et al., 2020. Social isolation, loneliness, socioeconomic status, and health-risk behaviour in deprived neighbourhoods in denmark: A cross-sectional study. SSM-population health 10: Article # 10054.

Applebaum JW et al., 2021. Love, fear, and the human-animal bond: On adversity and multispecies relationships. Comprehensive psychoneuroendocrinology 7: Article # 100071.

Arora G and Gupta S, 2017. Effect of human animal bond on emotional regulation and level of depression: A study of adolescence. International Journal of Research in Engineering 07: 58-62.

Bauman A et al., 2011. International perspectives on the epidemiology of dog walking. In: Johnson RA, Beck AM, McCune S, editors. The health benefits of dog walking for people and pets. Purdue University Press, West Lafayette; pp: 25-50.

Beetz A et al., 2012. Psychosocial and psychophysiological effects of human-animal interactions: The possible role of oxytocin. Frontiers in psychology 3: 1-15.

Beetz A, 2012. Positive wirkungen von tieren auf den menschen. Hunde im Schulalltag: Grundlagen und Praxis, Ernst Reinhardt, München, EU.

Bennett PC, 2011. Animals in our lives: Human–animal interaction in family, community, and therapeutic settings. Anthrozoös 24: 432-435.

Bolstad CJ et al., 2021. The relation between pet ownership, anxiety, and depressive symptoms in late life: Propensity score matched analyses. Anthrozoös 34: 671-684.

Braje TJ, 2011. The Human–Animal Experience in Deep Historical Perspective. In: Blazina C, editors. The Psychology of the Human-Animal Bond. Springer; pp: 62–80.

Brodeur A et al., 2021. Covid-19, lockdowns and well-being: Evidence from google trends. Journal of public economics 193: Article # 104346.

Brooks HL et al., 2018. The power of support from companion animals for people living with mental health problems: A systematic review and narrative synthesis of the evidence. BMC psychiatry 18: 1-12.

Brown SW and Goldstein LH, 2011. Can seizure-alert dogs predict seizures? Epilepsy research 97: 236-242.

Bryan JL et al., 2014. Canine comfort: Pet affinity buffers the negative impact of ambivalence over emotional expression on perceived social support. Personality and Individual Differences 68: 23-27.

Carpenter A et al., 2022. Vaccine preventable zoonotic diseases: Challenges and opportunities for public health progress. Vaccines 10: Article # 993.

Cevizci S et al., 2013.Animal assisted therapy and activities in alzheimer disease. In: Inga Z, editor. Understanding alzheimer disease. Tech Publishing: Rijeka, Croatia; pp: 303-320.

Chandler M et al., 2017. Obesity and associated comorbidities in people and companion animals: A one health perspective. Journal of comparative pathology 156: 296-309.

Coren S, 2002. For the Love of Dog and Other Beasts. In: Andy B, editor. The pawprints of history: Dogs in the course of human events. EC phsycological enterprises; pp: 143-155.

Dall PM et al., 2017. The influence of dog ownership on objective measures of free-living physical activity and sedentary behaviour in community-dwelling older adults: A longitudinal case-controlled study. BMC public health 17: 1- 9.

Dhont K et al., 2019. Rethinking human-animal relations: The critical role of social psychology. Group Processes and Intergroup Relations 22: 769-784.

Dowsett E et al., 2020. Adult separation anxiety disorder: The human-animal bond. Journal of Affective Disorders 270: 90-96.

Duncan C et al., 2020. Veterinary-prescribed physical activity promotes walking in healthy dogs and people. BMC veterinary research 16: 1-9.

Ellingsen K et al., 2014. Using qualitative behaviour assessment to explore the link between stockperson behaviour and dairy calf behaviour. Applied Animal Behaviour Science 153: 10-17.

Gee NR et al., 2010. Preschool children require fewer instructional prompts to perform a memory task in the presence of a dog. Anthrozoös 23: 173-184.

Gee NR et al., 2007. The role of therapy dogs in speed and accuracy to complete motor skills tasks for preschool children. Anthrozoös 20: 375-386.

Gourkow N et al., 2014. Effect of gentle stroking and vocalization on behaviour, mucosal immunity and upper respiratory disease in anxious shelter cats. Preventive Veterinary Medicine 117: 266-275.

Headey B and Grabka MM, 2007. Pets and human health in germany and australia: National longitudinal results. Social Indicators Research 80: 297-311.

Hediger K and Beetz A, 2015. The role of humananimal interactions in education. In: Zinsstag J, eiditor. One health: The theory and practice of integrated health approaches. Wallingford; pp: 73-84.

Hediger K and Turner DC, 2014. Can dogs increase children's attention and concentration performance? A randomised controlled trial. Human Animal Interaction Bulletin 2: 21-39.

Hui Gan GZ et al., 2020. Pet ownership and its influence on mental health in older adults. Aging and mental health 24: 1605-1612.

Hunjan UG and Reddy J, 2020. Why companion animals are beneficial during covid-19 pandemic. Journal of Patient Experience 7: 430-432.

Ikram S, 2015. Divine creatures: Animal mummies in ancient egypt. the American University in Cairo press, New York, USA.

Jones MG et al., 2019. Incorporating animal-assisted therapy in mental health treatments for adolescents: A systematic review of canine assisted psychotherapy. PloS one 14: Article # 0210761.

Krause-Parello CA, 2012. Pet ownership and older women: The relationships among loneliness, pet attachment support, human social support, and depressed mood. Geriatric Nursing 33: 194-203.

Kretzler B et al., 2022. Pet ownership, loneliness, and social isolation: A systematic review. Social psychiatry and psychiatric epidemiology 57: 1935-1957.

Lerner H, 2019. A proposal for a comprehensive human–animal approach of evaluation for animal-assisted interventions. International Journal of Environmental Research and Public Health 16: Article # 4305.

Levine GN et al., 2013. Pet ownership and cardiovascular risk: A scientific statement from the american heart association. Circulation 127: 2353-2363.

Lönker NS et al., 2020. Horses as a crucial part of one health. Veterinary Sciences 7: Article # 28.

Mani I and Maguire JH, 2009. Small animal zoonoses and immuncompromised pet owners. Topics in companion animal medicine 24: 164-174.

Matchock RL, 2015. Pet ownership and physical health. Current Opinion in Psychiatry 28: 386-392.

McCabe BW et al., 2002. Resident dog in the alzheimer's special care unit. Western journal of nursing research 24: 684-696.

McCune S et al., 2014. Evolution of research into the mutual benefits of human–animal interaction. Animal Frontiers 4: 49-58.

Meehan M et al., 2017. Using attachment theory and social support theory to examine and measure pets as sources of social support and attachment figures. Anthrozoös 30: 273-289.

Melson GF and Fine AH, 2015. Animals in the lives of children. In: Fine AH, editore. Handbook on animal-assisted therapy. Elsevier: Academic Press; pp: 179-194.

Mota-Rojas D et al., 2020. Effects of human-animal relationship on animal productivity and welfare. Journal of Animal Behaviour and Biometeorology 8: 196-205.

Mueller MK et al., 2018. Human-animal interaction as a social determinant of health: Descriptive findings from the health and retirement study. BMC public health 18: 1-7.

Napolitano F et al., 2020. The human− animal relationship in dairy animals. Journal of Dairy Research 87: 47-52.

O'Neil J, 2018. Zoonotic infections from common household pets. The Journal for Nurse Practitioners 14: 363-370.

Overgaauw PA et al., 2020. A one health perspective on the human–companion animal relationship with emphasis on zoonotic aspects. International Journal of Environmental Research and Public Health 17: Article # 3789.

Parenti et al., 2013. A revised taxonomy of assistance animals. Journal of rehabilitation research and development 50: Article #745.

Petersson M et al., 2017. Oxytocin and cortisol levels in dog owners and their dogs are associated with behavioral patterns: An exploratory study. Frontiers in psychology 8: Article # 1796.

Purewal R et al., 2017. Companion animals and child/adolescent development: A systematic review of the evidence. International Journal of Environmental Research and Public Health 14: Article # 234.

Rault et al., 2020. The power of a positive human–animal relationship for animal welfare. Frontiers in Veterinary Science 7: Article # 590867.

Robino AE, 2019. The human-animal bond and attachment in animal-assisted interventions in counseling. PhD Dissertation, Virginia Polytechnic Institute and State University.

Rushen J and Passille AM, 2015. The importance of good stockmanship and its benefits to animals. In: Grandin T, editore. Improving animal welfare: A practical approach. CAB International; pp: 125-138.

Segerstrom SC, 2008. Social networks and immunosuppression during stress: Relationship conflict or energy conservation? Brain, behavior, and immunity 22: 279-284.

Serpell JA, 2010. Animal-assisted interventions in historical perspective. In: Fine AH, editor. Handbook on animal-assisted therapy. Elsevier: Academic Press; pp: 17-32.

Shoesmith E et al., 2021. The influence of human–animal interactions on mental and physical health during the first covid-19 lockdown phase in the UK: A qualitative exploration. International Journal of Environmental Research and Public Health 18: Article # 976.

Smith B, 2012. The'pet effect': Health related aspects of companion animal ownership. Australian family physician 41: 439-442.

Stull JW et al., 2015. Reducing the risk of pet-associated zoonotic infections. Canadian Medical Association Journal 187: 736-743.

Stull JW et al., 2013. Pet husbandry and infection control practices related to zoonotic disease risks in ontario, canada. BMC public health 13: 1-15.

Svizzero S, 2016. Hunting strategies with cultivated plants as bait and the prey pathway to animal domestication. International Journal of Research in Sociology and Anthropology 2: 53-68.

Taylor M et al., 2015. The preparedness and evacuation behaviour of pet owners in emergencies and natural disasters. Australian Journal of Emergency Management 30: 18-23.

Tedeschi P et al., 2015. Treating human trauma with the help of animals: Trauma informed intervention for child maltreatment and adult post-traumatic stress. In: Fine AH, editor. Handbook on animal-assisted therapy. Elsevier: Academic Press; pp: 305-319.

Teo JT and Thomas SJ, 2019. Psychological mechanisms predicting wellbeing in pet owners: Rogers' core conditions versus bowlby's attachment. Anthrozoös 32: 399-417.

Thodberg K, 2014. Research in the use of animals as a treatment for humans. Animal Frontiers 4: 43-48.

Thompson K, 2013. Save me, save my dog: Increasing natural disaster preparedness and survival by addressing human-animal relationships. Australian Journal of Communication 40: 123-136.

Thompson K, 2018. Facing disasters together: How keeping animals safe benefits humans before, during and after natural disasters. OIE Revue scientifique et technique-office international des epizooties 37: 223-230.

Van Herten J and Meijboom F, 2019. Veterinary responsibilities within the one health framework. Food ethics 3: 109-123.

Waiblinger S et al., 2006. Assessing the human–animal relationship in farmed species: A critical review. Applied Animal Behaviour Science 101: 185-242.

Walczak M et al., 2012. Impact of individual training parameters and manner of taking breath odor samples on the reliability of canines as cancer screeners. Journal of veterinary behavior 7: 283-294.

Warburton DE and Bredin SS, 2017. Health benefits of physical activity: A systematic review of current systematic reviews. Current opinion in cardiology 32: 541-556.

Wei-Haas M, 2018. 40,000-year-old cave art may be world's oldest animal drawing. National Geographic. Published 7 November 2018. Accessed July 1, 2020.

Wells DL et al., 2008. Canine responses to hypoglycemia in patients with type 1 diabetes. The Journal of Alternative and Complementary Medicine 14: 1235-1241.

Winkle M et al., 2020. Dog welfare, well-being and behavior: Considerations for selection, evaluation and suitability for animal-assisted therapy. Animals 10: Article # 2188.

Zinn SA and Beck AM, 2014. The human–animal bond and domestication: Through the ages… animals in our lives. Animal Frontiers 4: 5-6.

33

Plastics and Microbiome: Impacts and Solutions

AUTHORS DETAIL

Sara Omer Swar

Food Technology Department, Collage of Agriculture Engineering Sciences, Salahuddin University, Erbil, Iraq
*Corresponding author: sara_swar@yahoo.com

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INTRODUCTION

In 1907, the very first commercial production of plastic was held after a Belgian chemist named Leo Baekeland invented 'Bakelite' in Yonkers, New York. After the First World War, lack of actual reliable resources along with a dire need of enhancement in technological tools drove technologists and researchers to develop unique and upgraded synthetic materials which included plastics as well. Nowadays, plastics embody an enormously huge group of synthetic and semi-synthetic polymer matter. These polymeric materials are fused with an abundant number of additives which tend to enhance the unique properties and performance efficiencies of the final products. Examples of these additives include plasticisers (to make the product a bit softer and more flexible), flame reductants (to reduce flammability of the product), and antioxidants (to reduce the chances of oxidation and production of free radicals which lead to degradation of the product) (Lithner et al. 2011).

Types of Plastics

Mainly, plastics were made by using natural fossil fuels like oil and gas but there are other types of production of plastics out there as well which differentiate on the basis of raw components used in their manufacturing.

(a) First one is the **'Bio-based plastics'** which comprises renewable resources like sugar beet and corn starch as the key components for its manufacturing (Geyer 2020).

(b) The second one is **'Drop-in plastics'** which can be made using any of the resources (either non-renewable like oil and natural gas or renewable like corn starch and sugar beet) (Geyer 2020).

In this day and age, plastics have become an undeniably crucial part of our daily life. In spite of the availability of a large number of options to be used in manufacturing of plastics, only eight of them make 95% of the primary mass production of plastics ever produced. Out of these eight key components, only two, polypropylene and polyethylene, have withheld 45% of the global plastics manufacturing (Geyer 2020).

Use of Plastics

36% of the total manufactured plastics are used for packaging and cramming which is basically the primary motive and use of plastics. At the second number, comes the use of plastics in construction and building (Geyer et al. 2017). Presently, the largely used plastics are completely fossil fuel based which are not biodegradable in their shelf life. Very small fraction, about 1% of the total manufactured plastics being used commercially come from bio-based resources (Geyer 2020).

Fate of Plastics

The three fates of plastic include recycling (10%), incineration (14%) and discarding (76%). As the climax of plastics hasn't really kept up with environmental safety, it results in mass contamination and globally widespread environmental pollution (Geyer 2020). If no precautionary measures are taken in regard to preventing the dumping of plastic wastes out in the open, it has been estimated that 710 million tonnes of plastic wastes will have contaminated our precious environment by the year 2040 (Lau et al. 2020).

Microplastics

Considering the largest leakages of plastics into the environmental pollution pool, it comes to mind what about the microplastics leakage into the environment which completely comes from daily life use of plastics and is shredded into the environment by wear and tear of daily used plastic products like tyres, ropes and clothing as well. The fragments of plastic shred into the environment with size smaller than one micrometre are referred to as microplastics (Toussaint et al. 2019). And by 2040, the expected leakage of the microplastics into the environment will grow by 1.3 to 2.5 times and there will be approximately 3 million trillion pieces of microplastics lying out there in the environment (Lau et al. 2020).

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The admittance of plastics of all sorts and forms at the current rate means that they're widespread across the globe in all types of ecosystems and are found in all types of matter on Earth. Evidence of the presence of plastics have been found in rivers and streams (Kelly et al. 2020) (Hoellein et al. 2017); mountain tops (Bergmann et al. 2019); deep ocean trenches (Chiba et al. 2018) (Van Cauwenberghe et al. 2013); and from tropics (Lamb et al. 2018) till the poles (Laganà et al. 2019).

Impacts of Plastic Pollution on Gut & Environmental Microbiome

It is sort of unfeasible to comprehend the impacts of plastic pollution globally on the microbiome but recently what has caught the attention of media around the globe is the death of Cuvier's beaked whale in the Philippines. The necropsy of this whale exposed the 40kg plastics waste in its stomach which was the leading cause of death of this precious marine animal (Borunda 2019). Another death of a young sperm whale on the Scottish beach led to the necropsy of the animal that exposed about 100 kg of the plastic wastes spread in its body (Beachum 2019). This led the researchers to conclude that countless lives of marine animals have been affected and lost due to plastic pollution in all water bodies (Brentano and Petry 2020; Moore et al. 2020; Deudero and Alomar 2015).

Scientists have found evidence that from sea snails (Li et al. 2020) to apex marine predators (Nelms et al. 2019; Santos et al. 2020), about 800 animal species have already been showing the symptoms of being affected from the plastics ingestion. Wilcox suggested that about 90% of all the sea birds found in marine life have shown evidence of ingesting plastics (Wilcox et al. 2015). The term 'microbiome' refers to the microorganisms living in a specified environment including its genome or community. But as there is ongoing research on all sorts and types of microbiomes, many researchers refer it as 'gut microbiome' because of the fact that plastic wastes of all kinds ultimately get to interact with the gut microbiome one way or another (Browne et al. 2008; Farrell and Nelson 2013; Nelms et al. 2018). The notorious impacts of plastics on both gut as well as environmental microbiome are known to be multiple in number (Fig. 1).

(i) Source of Organic Carbon

Some plastic wastes have certain additives or components which consist of organic carbon reservoirs that can be easily degraded by certain specific microorganisms, but it is limited to only a few taxa (Gambarini et al. 2020). This degradation process is really very slow and, in some cases, it hasn't been proven with facts yet or there's a dispute going on in some aspects. But it has been proven with facts and evidence that many plastic polymers like polyvinyl chloride, polystyrene, nylon, polypropylene and polyethylene can be degraded by microbiome (Danso et al. 2019).

(ii) Effect of Additives in Plastic

Largely pure plastic polymers are known to have a benign effect and have very low toxic effects on the biological systems. But the industrial plastics have additives like UV stabilizers, plasticisers and flame reductants which tend to alter the composition and functional characteristics of the microbial communities in ecological systems (Tetu et al. 2019). Direct consumption of Bisphenol A (a plasticiser) will be the active and direct cause of dysbiosis of the gut microflora causing damage to the health of the host (Feng et al. 2020).

(iii) Dispersal by Transport

As plastics provide a surface for attachment to the microorganisms, it also seems to affect the rate of flow at which a community of microorganisms disperse in a given environment. This way microbiomes can move both around the globe and from one part of the gut to another with the help of the plastics (Round and Mazmanian 2009).

These are just the direct impacts of plastics on microbiomes in the gut and in the environment. There is far less that we'd understand about the indirect ways that plastics can impact both gut and environmental microbiomes (Round and Mazmanian 2009).

Assuagement of plastic pollution by gut microbiomes

Several insect species have been found that harbor and wield the capabilities to ingest and decompose / degrade a wide range of polymers in the plastic wastes manually. Examples of these insect species include larvae of meal moths, wax moths and darling beetles. The larvae of Indian meal moths appear to be wielding the properties to degrade polystyrene (Yang et al. 2014). The same properties for degradation of polystyrene are also withheld by larvae of yellow and giant mealworms (Peng et al. 2019; Yang et al. 2020). Larvae of greater wax moths have been reported to be capable of degrading polyethylene (Lou et al. 2020). Furthermore, the larvae of lesser wax moths appear to have potential for degradation of polystyrene (Kundungal et al. 2019).

Isotopes analysis after necropsies of many dead marine animals have revealed the evidence that carbon from the plastics, in the form of polyethylene, incorporates and stays in the biomass of the invertebrate species of marine environment too (Taipale et al. 2019). Despite these findings and continuous research going on in this domain, it still remains uncertain to which extent an organism can degrade the plastic wastes in its system with the help of its microflora.

Many animals of various species accidentally ingest plastics but fail to gain any nutritive value from it. The residues of plastic wastes have been found in the gut of seabirds (Wilcox et al. 2015), fish (Lusher et al. 2013),

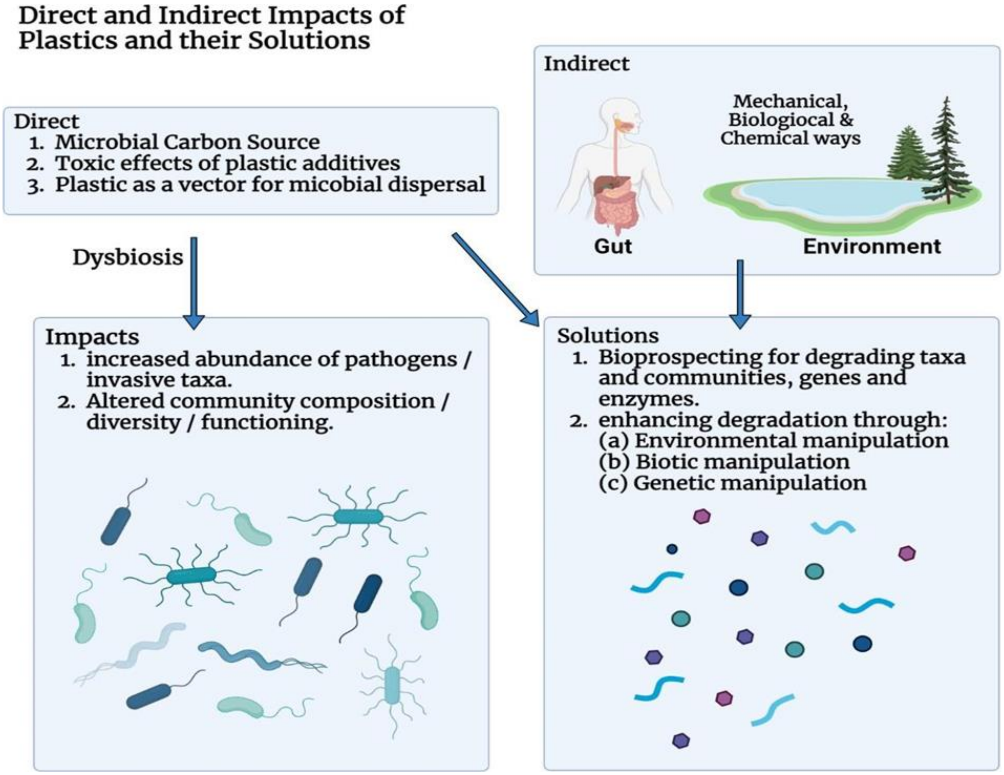
Direct and Indirect Impacts of Plastics and their Solutions
Direct
1. Microbial Carbon Source
2. Toxic effects of plastic additives
3. Plastic as a vector for micobial dispersal
Dysbiosis
Indirect
Mechanical, Biologiocal & Chemical ways
Gut
Environment
Impacts
1. increased abundance of pathogens / invasive taxa.
2. Altered community composition / diversity / functioning.
Solutions
1. Bioprospecting for degrading taxa and communities, genes and enzymes.
2. enhancing degradation through:
(a) Environmental manipulation
(b) Biotic manipulation
(c) Genetic manipulation

Fig. 1: Schematic highlighting of the diversity of Direct and Indirect impacts of plastics for Gut and Environmental microbiome communities and possible microbial solutions for the remediation of plastic wastes.

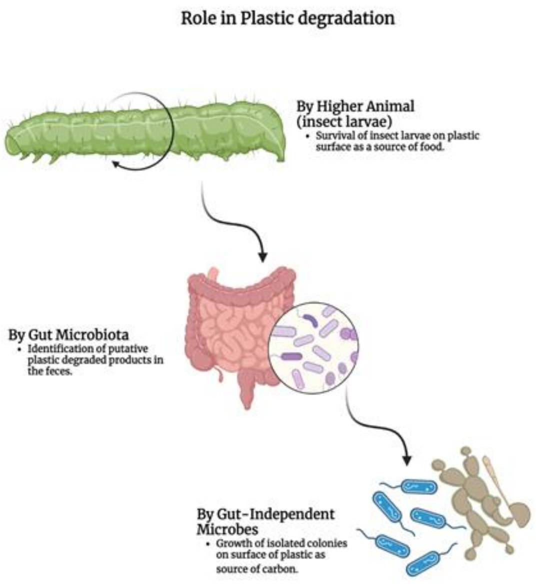
Role in Plastic degradation
By Higher Animal (insect larvae)
• Survival of insect larvae on plastic surface as a source of food.
By Gut Microbiota
• Identification of putative plastic degraded products in the feces.
By Gut-Independent Microbes
• Growth of isolated colonies on surface of plastic as source of carbon.

Fig. 2: Evidence for the role of insects, host-associated microbiome and host-independent microbiome in plastic degeneration.

marine worms (Wright et al. 2013), freshwater worms (Hurley et al. 2017) and zooplankton (Cole et al. 2013). Common earthworm is known to have the effective ability to reduce the size of plastic pieces that have been ingested into the gut (Huerta Lwanga et al. 2016). Although many animals degrade plastic in their gut either by conversion into carbon dioxide or by incorporating it into their biomass, these ways are unsubstantiated (Yang et al. 2015).

Palliation of plastic pollution by environmental microbiome

In 1974, the very first evidence, that free-living environmental microbiomes are also capable of plastic degradation, was brought to light by Fields and his associate researchers (Fields et al. 1974) about 30 years after the commercial manufacturing unit of plastic began to work. Fields' work revealed that a fungus *'Aureobasidium pullulans'* has the potential to actively degrade Polycaprolactone. This research study laid the basis for further research to be held in this domain regarding the search for a better, feasible and renewable way to degrade plastic wastes. After this study, plenty of names of microorganisms were mentioned to have the power of plastic degradation. A recent study (Gambarini et al. 2020) has reported that over 400 publications wholly conclude that there are 436 different species of fungi and bacteria that can degrade 72 different types of plastic polymers. The important fungal and bacterial phyla that are termed as plastic-

Table 1: Plastic-degraders belonging to different phyla of Bacterial and Fungal microorganisms along with the number of species per phylum that can degrade plastic as Environmental microbiome.

No.	Bacteria		Fungi	
	Phylum	No. of species	Phylum	No. of species
1.	Bacteroidetes	003	Ascomycota	118
2.	Proteobacteria	133	Basidiomycota	019
3.	Actinobacteria	088	Mucoromycota	013
4.	Cyanobacteria	002		
5.	Firmicutes	060		

degraders have been enlisted in Table 1. A small number of microbes isolated from different plant and animal species have been reported to be plastic-degraders (Koitabashi et al. 2012; Almeida et al. 2019; Zhang et al. 2020).

Conclustion

The global plastic pollution has diverse impacts on both gut and environmental microbiomes which is found entangled in ranging from direct impact of the toxic leachates on the health and activity of the microbial community to the indirect interaction of plastics with the environment and host organisms. There are hundreds of the microbial species which are found entangled along with their genomes and enzymatic metabolism to the degradation of plastic wastes. Talking about smaller quantities of bio-based plastics, for example PLA, have shown clear cut evidence regarding their microbial degradation both in the gut and environment. However, considering the major commercially produced plastic products, there hasn't been enough evidence to point out that they can be degraded using microbial degradation processes as a weapon to wipe plastic wastes off the face of Earth. Many scientists have tried but failed to prove that microbes can completely degrade plastic wastes. More research is required in order to make sure that both gut and environmental microbiome can degrade the plastic wastes.

REFERENCES

Almeida EL et al., 2019. In silico screening and heterologous expression of a polyethylene terephthalate hydrolase (PETase)-like enzyme (SM14est) with polycaprolactone (PCL)-degrading activity, from the marine sponge-derived strain Streptomyces sp. SM14. Frontiers in Microbiology 10: 2187.

Beachum L, 2019. Dead sperm whale had 220 pounds of garbage in its stomach, including rope, plastic and gloves. Wahington DC: The Washington Post.

Bergmann M et al., 2019. White and wonderful? Microplastics prevail in snow from the Alps to the Arctic. Science Advances 5(8): 1157.

Borunda A, 2019. This young whale died with 88 pounds of plastic in its stomach. National Geographic Magazine.

Brentano R and Petry MV, 2020. Marine debris ingestion and human impacts on the pygmy sperm whale (Kogia breviceps) in southern Brazil. Marine Pollution Bulletin 150: 5.

Browne MA et al., 2008. Ingested microscopic plastic translocates to the circulatory system of the mussel, Mytilus edulis (L). Environmental Science and Technology 42(13): 5026–5031.

Chiba S et al., 2018. Human footprint in the abyss: 30 years records of deep-sea plastic debris. Marine Policy 96: 204–212.

Cole M et al., 2013. Microplastic ingestion by zooplankton. Environmental Science and Technology 47(12): 6646–6655.

Danso D et al., 2019. Plastics: environmental and biotechnological perspectives on microbial degradation. Applied and Environmental Microbiology 85(19): 14.

Deudero S and Alomar C, 2015. Mediterranean marine biodiversity under threat: reviewing influence of marine litter on species. Marine Pollution Bulletin 98(1-2): 58–68.

Farrell P and Nelson K, 2013. Trophic level transfer of microplastic: Mytilus edulis (L.) to. Carcinus maenas (L.). Environmental Pollution 177: 1–3.

Feng D et al., 2020. Bisphenol A exposure induces gut microbiota dysbiosis and consequent activation of gut-liver axis leading to hepatic steatosis in CD-1 mice. Environmental Pollution 265: 114880.

Fields RD et al., 1974. Microbial degradation of polyesters: Polycaprolactone degraded by P. pullulans. Journal of Applied Polymer Science 18: 3571–3579.

Gambarini V et al., 2020. An updated phylogenetic distribution for plastic-degrading organisms and enzymes.

Geyer R, 2020. Production, use, and fate of synthetic polymers. Plastic Waste and Recycling. Oxford: Academic Press; 13–32.

Geyer R et al., 2017. Production, use, and fate of all plastics ever made. Science Advances 3(7): e1700782.

Hoellein TJ et al., 2017. Longitudinal patterns of microplastic concentration and bacterial assemblages in surface and benthic habitats of an urban river. Freshwater Science 36(3): 491–507.

Huerta Lwanga E et al., 2016. Microplastics in the terrestrial ecosystem: implications for Lumbricus terrestris (Oligochaeta, Lumbricidae). Environmental Science and Technology 50: 2685–2691.

Hurley RR et al., 2017. Ingestion of microplastics by freshwater tubifex worms. Environmental Science and Technology 51(21): 12844–12851.

Kelly JJ et al., 2020. Microplastic selects for convergent microbiomes from distinct riverine sources. Freshwater Science 39(2): 281–291.

Koitabashi M et al., 2012. Degradation of biodegradable plastic mulch films in soil environment by phylloplane fungi isolated from gramineous plants. AMB Express 2(1): 40.

Kundungal H et al., 2019. Efficient biodegradation of polyethylene (HDPE) waste by the plastic-eating lesser wax worm (Achroia grisella). Environmental Science and Pollution Research 26: 18509–18519.

Laganà P et al., 2019. Do plastics serve as a possible vector for the spread of antibiotic resistance? First insights from bacteria associated to a polystyrene piece from King George Island (Antarctica). International Journal of Hygiene and Environmental Health 222(1): 89–100.

Lamb JB et al., 2018. Plastic waste associated with disease on coral reefs. Science 359(6374): 460–462.

Lau WWY et al., 2020. Evaluating scenarios toward zero plastic pollution. Science 369(6510): 1455-1461.

Li RL et al., 2020. Field study of the microplastic pollution in sea snails (Ellobium chinense) from mangrove forest and their relationships with microplastics in water/sediment located on the north of Beibu gulf. Environmental Pollution 2020; 263:268.

Lithner D et al., 2011. Environmental and health hazard ranking and assessment of plastic polymers based on chemical composition. Science of the Total Environment 409(18): 3309–3324.

Lou Y et al., 2020. Biodegradation of polyethylene and polystyrene by greater wax moth larvae (galleria mellonella L.) and the effect of co-diet supplementation on the core gut microbiome. Environmental Science and Technology 54(5): 2821–2831.

Lusher AL et al., 2013. Occurrence of microplastics in the gastrointestinal tract of pelagic and demersal fish from the English Channel. Marine Pollution Bulletin 67(1-2): 94–99.

Moore RC et al., 2020. Microplastics in beluga whales (Delphinapterus leucas) from the eastern Beaufort Sea. Marine Pollution Bulletin 150: 7.

Nelms SE et al., 2018. Investigating microplastic trophic transfer in marine top predators. Environmental Pollution 238: 999–1007.

Nelms SE et al., 2019. What goes in, must come out: combining scat-based molecular diet analysis and quantification of ingested microplastics in a marine top predator. Methods in Ecology and Evolution 10(10): 1712–1722.

Peng BY et al., 2019. Biodegradation of polystyrene by dark (Tenebrio obscurus) and yellow (Tenebrio molitor) mealworms (Coleoptera: Tenebrionidae). Environmental Science and Technology 53(9): 5256–5265.

Round JL and Mazmanian SK, 2009. The gut microbiota shapes intestinal immune responses during health and disease. Nature Reviews Immunology 9(5): 313–323.

Santos RG et al., 2020. Exploring plastic-induced satiety in foraging green turtles. Environmental Pollution 265: 114918.

Taipale SJ et al., 2019. Tracing the fate of microplastic carbon in the aquatic food web by compound-specific isotope analysis. Scientific Reports 9: 19894.

Tetu SG et al., 2019. Plastic leachates impair growth and oxygen production in Prochlorococcus, the ocean’s most abundant photosynthetic bacteria. Communications Biology 2: 184.

Toussaint B et al., 2019. Review of micro- and nanoplastic contamination in the food chain. Food Additives and Contaminants 36(5): 639–673.

Van Cauwenberghe L et al., 2013. Microplastic pollution in deep-sea sediments. Environmental Pollution 182: 495–499.

Wilcox C et al., 2015. Threat of plastic pollution to seabirds is global, pervasive, and increasing. Proceedings of the National Academy of Sciences of the United States of America 112(38): 11899–11904.

Wright SL et al., 2013. Microplastic ingestion decreases energy reserves in marine worms. Current Biology 23(23): 1031–1033.

Yang J et al., 2014. Evidence of polyethylene biodegradation by bacterial strains from the guts of plastic-eating waxworms. Environmental Science and Technology 48(23): 13776–13784.

Yang Y et al., 2015. Biodegradation and mineralization of polystyrene by plastic-eating mealworms: part 2. Role of gut microorganisms. Environmental Science and Technology 49(20): 12087–12093.

Yang Y et al., 2020. Biodegradation and mineralization of polystyrene by plastic-eating superworms Zophobas atratus. Science of the Total Environment 708: 7.

Zhang JQ et al., 2020. Biodegradation of polyethylene microplastic particles by the fungus Aspergillus flavus from the guts of wax moth galleria mellonella. Science of the Total Environment 704: 8.